MYCOSES OF MAN AND ANIMALS



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Foreword

At the time of his death in 1950 Dr Maurice Langeron had been engaged in preparing a second edition of his admirable *Précis de Mycologie*. The completion of this work then devolved on his friend and former pupil Professor R. Vanbreuseghem. In the new edition, published in 1952, the work was divided into three parts. The first, on General Mycology, represented the greater part of the original book and preserved its outstanding characteristics. Descriptions of technical procedures were collected together and formed the second part. The third part, devoted to Medical Mycology, was an entirely new feature contributed by Professor Vanbreuseghem which greatly enhanced the value of the book. This part, which has been translated into English by Dr J. Wilkinson, is the subject of the present publication.

The translation has been made as literal as is feasible and the subject is presented to the English reader without addition to or alteration of the original text.

JACQUES WALKER

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Preface

FROM THE VANBREUSEGHEM INTRODUCTION TO THE SECOND EDITION OF LANGERON, *Précis de Mycologie*

l m mo pt t f n pol
Il el q o l po nt
Terer (Ant an)

WHEN in July 1950 Mme Langeron and Dr Langeron formally entrusted me with the preparation of the second edition of the *Précis de Mycologie* I accepted with hesitation for fear of detracting from the value of my master's work. I expected to have at my disposal the manuscript to which Dr Langeron had told me he had devoted himself since the publication of the seventh edition of his *Précis de Microscopie*. It proved however impossible to find the essential document. I had therefore to be content with what Mme Langeron was kind enough to hand over to me: an interleaved copy of the first edition of the *Précis de Mycologie* together with numerous offprints or microfilms collected with a view to the second edition. This material together with what I personally possessed formed the basis of the book I am now privileged to present.

The first edition comprised eleven chapters. I have divided them into three sections: General Mycology, Technique and Medical Mycology. General Mycology is based essentially on the first edition but the distribution of the material has been considerably modified. Additions have been made to it from Dr Langeron's notes and from my own reading. The second part devoted to technique follows the plan previously adopted but has been supplemented by new procedures which have appeared since 1945. For the third part, Medical Mycology, I take full responsibility. This topic was, in the first edition, limited to Chapter IX entitled 'What does medical mycology amount to?' This title must be regarded as an appropriate means of rounding off the volume but at the same time it showed clearly Dr Langeron's intention to put the reader on guard against those who are always ready to create new mycoses on the strength of some mould isolated from a refractory case. Dr Langeron used to say to me: 'When people don't know which way to turn [which saint to invoke] they think of fungi.' I have completely replaced this ninth chapter by an entirely new third part in which the mycoses are studied in alphabetical order. It consists of seventeen chapters. I have endeavoured to omit nothing essential even of the most recent work and I have wherever possible set out what is known of animal mycology.

I feel that in this form the second edition would in no way run counter to the views of my late friend.

It may seem paradoxical to say that a scientific book owes more to many others than to its author. It is however true and particularly of the present volume, which rests essentially on the work of Dr Langeron and on the experience of his long and fruitful career. Mme and Mlles Langeron have been extremely courteous in helping me gather the material necessary for this second edition and have greatly honoured me by entrusting me with the spiritual inheritance of one whom I knew well and so greatly admired.

Professor Edmond Sergent, whom I met when he visited the Pasteur Institute in Algiers, kindly undertook the introduction of the present work to French readers: a more eminent ambassador could scarcely be imagined, and I owe him a great debt of gratitude.

The Institute of Tropical Medicine at Anvers has put at my disposal its spacious laboratories and its remarkable library. For this I am indebted to its distinguished Director, Professor Dubois, to whom I tender my warmest thanks.

The interest shown by the Institute of Scientific Research in Central Africa (I.R.S.A.C.) in numerous branches of science led it to trust me with the carrying out of investigations in the medical mycology of the Belgian Congo and to subsidize my research for several years. I particularly owe my thanks to M. le Ministre De Bruyne, President of I.R.S.A.C., Prof. J. Rodhain, President of the Commission of Human and Animal Pathology, Prof. L. Van Den Berghe, Director of I.R.S.A.C. in Africa, Prof. J. J. Harroy, General Secretary of I.R.S.A.C., and all the members of the Administrative Council.

Professors Gerard and Penaux of the University of Brussels have given me their constant moral support and Prof. A. Dalcq has given me much invaluable advice. I owe them my deepest gratitude.

My thanks are also due to Miss L. K. Georg (U.S.A.) and Dr M. [illegible] (Brazil) for the fine microphotographs they have allowed me to use.

Many doctors and public health inspectors in the Belgian Congo have helped me considerably by sending material. I am particularly indebted to Drs Borgers, Kivit, Lejeune and Mathieu, and to the Chief Inspector of Public Health, M. Doom. Mlle Van Hoof proved to be the most considerate of librarians and Mlle Van Reusel was a laboratory assistant and secretary an indispensable daily help. My best thanks are due to all.

I am also infinitely grateful for the care taken by M. [illegible] in publishing this book and for their courtesy and attention always.

My wife, who already had many claims to my affection, has now acquired even more of it by helping me materially and morally throughout the preparation of this work.

If I were allowed to dedicate the book, it would be to the memory of two remarkable men of science who both at different stages contributed to the development of my scientific career: Professor Andre [illegible]

Laig[illegible] who w[illegible] with Flemming pione[illegible] in the field of antibiotics [illegible]nd Dr Maurice Langeron whose *Préc[illegible] d[illegible] Microscopie* h[illegible] rendered and continues to render the great[illegible] t [illegible]ervice in laboratorie[illegible] all over the world

R. [illegible]

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[illegible] April 19[illegible]

Contents

CHAPTFI I

Mycoses caused by Actinomycetes

Introduction

At first glance it would seem improper to use the term tino my f l eases prod eed by members of the Actinomycetaceae but this is no long j t liable I the fir t place the designation actinomy oses tr litionally ref rs t the l wn d cervicofacial actinomycoses thi di   rs qu t differ t from other myco es caused by members of the Actinomy t cea   ex pt for certain mycetoma prod eed by actino mycetes Again the actinomycetes h e been so conf ed with one another that their precise t xonomy ha only recently been clarified by the work f Waksman nd H rici (1943) In this the Nocardiose were onsidered t be d stinct from l ecal   tinomycosi   Widespread ignorance of ert in fund mental haracteri tics of Actinomycet ceae g bether erobic or anaerobic acid fast or not ha in alidated much comp   ti ely recent worl The separation of   rtain li ea es included in thi   hapter (erythrasm   trichomyco) from the   tinomyco es and nocardiose is con idered to be justified not only on clinical ground but lso becau e of l k f information   t the real nature of their   usal agent   N   tt mpt will be made t ref r t the   ery intere ting anti biotic proj rties of ctinomycetes for this subject the outst nding work f W l ch (1947) should be con lted

Broadly speaking the actinomycet   are m cro orga sm pos ssing ither rudimentary mycelium or   w ll developed one not   ceeding one micron in diameter The former omprise the family Mycobacteria eae w th but one genus *Mycobacteri m* the e are bacteri   The latter with a true mycelium are nearer t th f ngi They omprise two families the A tinomy et ce e   which reprod ce by myceli l fragmentation and are di ided int tw gener   *Actinomyces* and *Nocardia* and the Strep tomy tacea   wh h reproduce by conid   nd comprise the tw g nera *Streptomyces* and *M cromono pora*   *Actinomyces* and *Nocardia*   will be de lt w th in due cour   The characters of the g nera *Streptomyces* and *Micromono pora* may here be summarized t   oid reject tion these two genera re included in the family Streptomycetaceae by Waksman and Henric (1943) who di ting i h them by the pos ssion of   vegetati mycelium wh h does not fragment int bacilliform or cocciform elements and reprod   by me   f spores

Gen   *Streptomyces* W l man nd Henric 1943 *Streptomy*   pecies

are undoubtedly the most wide pread of all Actinomycete According to Skinner Emmons and T uchiya (1948) they represent 20-50 per cent of the colonies obtained by spreading soil on agar but they are equally abundant in the atmo phere Mo t of the work on Actinomycete is really concerned with *Streptomyce* The e are aerobic non acid fa t form the mycelium of which fragments but little and which reproduce by onidia arranged in short chains The e are frequently of piral form and the conidiophores (porophore) are simple or branched In the soil they convert nitrates to nitrites break down proteins into simpler compound and attack chitin and carbohydrates of a complex a nature a starch and cellulo e They are not pathogenic f r man or animal but veral species attacl potato tubers (*Streptomyces* [*Actinomyces*] *scabie*) Th pecific identification of *Streptomyces* is very difficult not only becau the pecies characters have been poorly resolved but al o becau e only v ry few species have been adequately de cribed

The formation of spore in hort chains is one of the essential f tures of the genus Unfortunately the appearance of the e spore is not constant under all environmental conditions Jone (1949) ha hown recently that one fifth of the 1 205 isolates made from different oil exhibited no constant *morphology of the aerial mycelium* and that aft r the first incubation 0 per cent of the isolates formed only vegetativ mycelia whence arises the po ibility of confusion with the g nu *Nocardia*

Coret and Joubert (1951) have howe r i olated from a eptic n n actinomycosis of the do an actinomycete w th all the characters of *Streptomyce* (*S gall* *n*)

Genus *Micromono pora* Ørsko 19 3 *Micromono pora* includes a robic and non acid resi tant a tinomy t with repro lu ti e p res borne either singly upon the aerial mycelium or aggreg t l in ma es This is a y t a little known genus of which all the specie are app rently saprophytic and may be i lated from soil dung and le aving organic matter

Waksman and Henrici (1943) hav tabulated the hief charact risti of the actinomycetes a follows—

ORDER ACTI OMYCET LE

A Family **Mycobacteriaceae** Chester

Mycelium rudimentary or absent
Genus *Mycobact ri m* Lehmann and N m nn
Acid fast or anaerobic

B Families **Actinomycetaceae** and **Streptomycetaceae**

Formin a tru mycel um

I Family Actinomycet a Buchanan

Veg tativ my l m fragment int ba ill form or iform lament

( ) Gen *Act nomyce* Harz 1877

Anaerol or microaerophiles p ra tes Gr positiv non cid fa t

(*b*) Genus *Nocard* a Trevi n 1889

Aerobes Gram positi a id fast or non l f t

II Family Streptomycet ce W ksman and H n i

Veg t t my el not fragmenting int bacillif rm r occiform lament

( ) Genus *Streptomyce* W ksman nd Henric 1943

Reprod tion by conid a borne in small chains upo aeri l fil ment

(*b*) Genus *Micromono pora* Orskov 1 23

Reproduction by terminal spores borne singly upo short porophores

A ACTINOMYCOSIS

Definition

Act nomyco is chron disease caused by *Act nomyce* *srael* nd haracterized by a granul tion tissue which becomes and discharg through sinuses The pu frequently includes sulphur yellow gran les The di ea attack man and cattle

There appears to be general agreement on the desi nation f the disease but in the literature one occa ionally comes ero the n me trept thricosis nocardo is or nocardiosis This la t term must be kept for di ea caused b *Nocardia* specie The expres ion ctinomycotic mycetom h al o been used by Langeron (1930) t d ignate all d e aused by *Act nomyce* species which give a clinical pi ture of mycetom and t distingui h them from maduromycotic mycetoma caused by hyphomy etes Lignieres (1 4) and al Spit proposed the term Actinophyt is to designate all di ea es in which one find clubbed granule including the name of th microbe whi h causes them

Historical

The fir t case of human ctinomycosis ppears to hav been de ribed in 18 7 by Lebert since when in 1870 Bollinger described the disea in attle Harz in 1877 called the pathogenic a ent *Act nomyce bov* relying upon the origin and appea ance f the para te within the tissues but he did not obtain cultures In 1890 Bol trom i ol ted an erobic st ain which he on idered t be *A bov* Harz but which wa bviously not the organi m re pon ble for the cl ssical actinomycosis

I 1891 Wolff and I ra l ol ted under anaerobic condition of culture an *Act nomyce* hich Israel had previou ly isol ted in 1884 Kru in 1896 named this *Act nomyce* *sra l*

described by Grakov and bearing his name. This occurs as follows: after segmentation of the Actinomyces filaments the segments enlarge and repel one another by their ends so as to assume an angular configuration. The segmentation of the filaments is still very controversial and appears to be most clearly apparent in young colonies.

In tissues or exudates *Actinomyces israeli* takes the form either of branching Gram-positive and non-acid-fast filaments or of sulphur-yellow granules. These granules vary greatly in shape and dimensions. Frequently they are invisible to the naked eye but may sometimes be 1–2 mm in size. Their colour is traditionally described as sulphur-yellow (sulphur granules of English and American writers), but many describe them as white or yellowish-white. They are usually of soft consistency and may easily be crushed between cover-slip and slide. Occasionally, however, hard and calcified granules are encountered. It is only too frequently stated that the colonies of *Actinomyces israeli* are visible to the naked eye; in general this is incorrect, and a diagnosis of actinomycosis must not be rejected without a search for granules under the microscope. Moreover, the presence of these granules is not absolutely necessary for diagnosis.

Actinomycosis granules freshly pressed out under the cover-slip present on examination a polygonal or polycyclic appearance with, in the centre, a tangle of filaments which gradually open out towards the periphery, where they persist as what the French writers call *massues* and the English clubs. These clubs are acidophilic. By using Gram staining method it can be demonstrated that the filaments retain the gentian violet, whilst the modified Ziehl procedure shows that they are not acid-fast.

The clubs which envelop *the actinomycosis granule are not a constant* feature and are not indispensable for diagnosis of the disease. Granules both with and without clubs may indeed be found in the same pus. The origin of the clubs is still very debatable, but they may well represent a reaction on *the part of the organism sensitized towards* the pathogenic effect of the *Actinomyces israeli*. Certain workers, however, have apparently seen the clubs in culture.

It should be borne in mind that these clubs may be produced by *organisms other than Actinomyces israeli*, e.g. by staphylococci and by *Actinobacillus lignieresi*, and also by a great many other pathogenic fungi such as *Sporotrichum*, *Phialophora*, etc.

Symptomatology

Actinomycosis may be localized in many sites, the most frequent being the cervicofacial, pulmonary and abdominal. Besides these, the ... [illegible] forms have been described which are really due to *Nocardia* and which should not be included within the strict boundaries of the actinomycoses: the purely cutaneous form, the ocular and gastric forms, and ... [illegible]

Cervicofacial Actinomycosis

This is the most frequent form and was found in 56 8 per cent of the series of cases studied by Cope (1938) The lesion usually first appear upon a swelling in the angle f the lower jaw The skin over this swelling which soon becomes tough and woody i reddish iolet in colour The surface becomes irregul r and soon exudes pus from several openings In this pu occur the characteri tic granules

Often this is preceded by dent l trouble such a extraction or a tonsilectomy

The infection may extend to the pharynx and the orbit and there may be invasion of the salivary and lachrymal gland

Diagnosis present no difficulty

Pulmonary Actinomycosis

This is less frequent (— 3 per cent in Cope s series) and is seldom recognized before it has prod ced a fistular condition in the thoracic wall In the absence f me ns of scertaining its true diagnosis it most nearly simulates tuberculo is Signs of discharging pleurisy may be evident before the inf ction makes t external appearance but in most cases it is the development of a cutaneous bscess quickly followed by fistularization which perm t of diagnosis

In the pulmonary form w ll as in the abdominal form with which it may be confused there may be an emission of particles by w y of the buccal cavity which enclose the *Act nomyce srael* H we er both the pulmonary and the thoracic form may be derived one from the other nd the pulmonary may frequently complicat the bdominal form

Can *Act nomyce srael* be isolated from bronchial secretions in the absence of tinomycosis? This appears to ha e been confirmed in r cent and very interesting investigation by Kay (1948) This worker has searched systematically for *A srael* in patients with bronchiectasis chronic bscesses and suppuration xtending from the lung and has isolated it in 0 per cent of the cases The secretions were first obtained by bron hoscopy or from operat fragment In one quarter f the positive cases actinomycosis gra ule were found It is acknowledged that the presence of *Act nomyce* without necessarily prod cing the disease omplicates it and may lead t true actinomycosis with a char cteristic development of sinuses

Abdominal Actinomycosis

This would appear t be caused by the disintegration of particles containing *Act nomyce sra l* or t result from an xtension of the pulmonary form

This form (16 per cent of Cope s 1 330 cases) is scarcely e er diagnosed before a laparotomy or an autopsy The most frequent linical indication is pain resembling that of ppendicitis in the lower right region of the abdomen Palpation reveals soft lump in the ileocaecal region In th

absence of operation the infection may extend towards the muscle of the anterior abdominal wall and become fistular or it may get to the vertebral column attacking the vertebra and causing nervous troubles. A good many cases of *parametritis actinomycotica* have been described and amongst the various explanations Strange (1950) has pointed out the possibility of infection by an external route (repeated digital dilatation of the anus).

Histopathology

For a specific histopathological diagnosis actinomycotic granulation must be shown to be present in the tissues. Without these the picture is insufficiently complete to permit of diagnostic conclusion. The exceptional presence of delicate solitary filaments might incline the observer towards a diagnosis of actinomycosis. Stained with eosin haematoxylin the granules would show a deeper central region and a reddish periphery since the clubs have a special affinity for eosin.

The granules make up the centre of a granulation tissue where white globules, giant cells and *eosinophiles are found. Polymorphonuclear cells* the disintegration of which lead according to certain workers to the formation of clubs are most directly in contact with the granule.

Following up previous deductions there may be found a copious suppuration or an internal sclerosis. In either case in the absence of the typical granules a diagnosis of actinomycosis would not be warranted.

The use of Gram's staining procedure upon histological sections will differentiate any Gram positive filaments in the granule. If the granulation should be caused by *Actinobacillus lignieresi* the bacilliform elements within the granule are Gram negative. Should the granule be produced by a staphylococcus the form of the latter is easily recognised.

Treatment

Although certain claims have been made for the treatment of this mycosis by potassium iodide administered orally (3 drops of a saturated solution 3 times daily increased by 1 drop per day up to 20 drops 3 times daily) or sodium iodide intravenously (1 g p.d.) prognosis has been considerably modified by the introduction of sulphonamide and penicillin.

Surgery is of some value in removing irreparable damage (pulmonary, abdominal, ileo-appendicular and bony lesions, respectively) and X-rays in certain inflammatory conditions. Thus Lamb, Lain and Jones (1947) for cervicofacial actinomycosis administered 100 r for two weeks daily up to a total dose of 1,800–2,000 r at a distance 80 cm with 4–6 mm aluminium filter or 1 mm al minimum 0.5 mm [illegible] filter for kilovoltage 170–180.

The sulphamide preferably sulphadiazine may be administered for 4–6 months maintaining a level of 10 mg per cent. The dosage of which the active dose is not well established being about rapid and regular. In practice there is a tendency to combine penicillin and sulphamide.

Prognosis

The prognosis of actinomycosis i best in the purely cutaneous forms and good in the cervicofacial form it is frankly ba l the pulmonary and ldominal forms

On the whole wh t is known of the pro no is f tinomycosis ha emerge l from result obtained before the era of sulphamid and penicillin therapy and will doubtless be revised

Differential Diagnosis

Only the cervicofacial form f actinomycosi prese t a clinical picture hich can be recognized thi is not to say however that it diagno must be resol e l solely on a clinical bases It is t be expected that d ea of such hronic evolution and polymorph symptomat lo y a tinomycosi mu t inevitably be onfu ed with the most aried diseases from l c absc complicating n bdominal form and sim l ting a hepatic metastas t pulmonary tuberculosi or cerebral tumour

Mycological Diagnosis

This depend upon (i) the xamination of actinomycosis granules in the pu and (ii) the i ol tion of A isra l in culture The first patholo ical liagno is is less rele nt for ctinomycosi than for ther deeply seated my oses for it may often be replaced by careful xamination of the gran les in the pu

1 Examination of Granules in the Pus

I u may be obtained from the sinu diluted with physiolo i l line and examined n petri dish placed a a nst da k background or filt red on gauze As already mentioned granules are not alw y isible to the naked y and they occasionally tta n a size of 1 mm but never more than mm They should be carefully examined w th h nd len or whilst in the petri dish under the binocul microscope

Conant *et al* (1949) recommend the ppl cation on the sinuses f dry sterile gauze from the meshes f which gran les may be obtained the morn in after the pplication

The granule are small mass of irre la hape whitish or y llowish soft and exceptionally e leified

2 Culture of Actinomyces israeli

Cultures of *A israeli* are difficult to obtain because the parasite is anaerobic or m croaerophilous and though it may be easy t grow and isolat an anaerobe in pure culture or from pathological products which only contain anaerobes the isolation much more difficult from con tamin ted sources Further *A israel* is a del cat organism and xactin from the nutritional point of iew Lastly this parasite can only w th difficulty be maintained in the laboratory it requires frequent sub culture and even so the cultures eventually die Most workers seem unable t

maintain their strains *for more than 3–4 months* However accordi Rosebury (1944) if the strains die out in spite of persistent attemp maintain them upon a given medium they may be perpetuated easily by transplantation upon different media as *in a rotation*

Several media are suitable for the culture of *A israeli* for exa nutrient agar with the addition of 1 per cent glucose Dorsett medium or glycerine egg medium nutrient broth and a medium w has given Rosebury the best results namely Difco s Bacto brain infusion added to 2 per cent agar This culture medium which ha advantage of a relatively stable composition may also be improvi c any laboratory

A israeli varies from strain to strain and from one day to another i tolerance for oxygen but for satisfactory results it must alway *cultured under conditions of partial or total anaerobiosis*

The easiest method of ensuring partial anaerobiosis is to introduce material for culture into the bottom of a tube of nutrient broth or nutr agar to which has been added 1 *per cent glucose or Bacto brainb* infusion in 2 per cent agar kept at the bottom of the test tube liqu on the water bath and inoculated after cooling but before solidific of the agar (shake cultures) The actinomycosis granule colle under as sterile conditions as possible and washed in several cubic ce metres of physiological saline is placed in a first tube and crushed aga the side of the tube which is shaken to ensure the even distribution the granule fragments in the bulk of the liquid agar After thi portion of the agar is transferred to a second tube and this is repea to the extent of five or six tubes with the object of getting well isol colonies

The tubes are kept at 37 C and after 5 or 6 days are examined wit view to microscopical study of the colonies and further transplantati *The broth cultures lend themselves well for microscopical examinati* but on account of frequent contamination are of little use as a source pure colonies On the other hand agar cultures show well isolated colon developed a little below the surface good example have a particula abundant accumulation of colonies 1 cm below the surface By means a Pasteur pipette a white colony is withdrawn having a surface form by several biconvex lenses set at various angles (Crootten) and a fr is smeared out for staining by Gram s method for the recognition of inta branching Gram positive filaments or else bacilliform elements exhibiti the angular growth of Œrskov One or more colonies should be simult withdrawn *for transplantation*

If the inoculum is obviously very contaminated or if it is impossible isolate the granules the procedure recommended by Rosebury Epps an Clark (1944) is advised The Bacto brainheart infusion added to 2 p cent agar is introduced into petri dishes then 1 ml of sterile broth poured over the surface of the agar in each dish for better exposure Th material to be cultured is streaked on several (4) petri dishes *witho*

reckary ng the pl t n m loop The petri di hes are then placed at 37 C in a gla ves l enclo g 5 per cent CO and hydro en catalysed by warming er pl tinum or palladium After 4 t 6 day those colonies are first removed which are whit firm and deeply set in the culture med um (type R) f llowed by th soft and friable ones (type S) According to Rosebury the colonie are nearly ll type R when first isolated nd progress ely hang t type S by sub cult ring These occur at lower k ls f the g

Special care is needed witl colonies which naturally anaerobic o microaerophilous ha adapted themselves t free ai and seem able to maintain themselv there for they are likely without warning to requ re a return t non aerated medium from time t time

The opt m m temperature for the development of I i rael is 37 C At — C t will not grow W rming for 3 10 min tes t 6—4 will kill it will w rming for 1 hour t 60 C The optimum pH is 7 7 6

Sugar i not fermented w th ga production but the action of I israel on several sugars (glucose lactose maltose manno e sucrose) results in acidification of the medium The proteolyt action of the ultures indole formation r d ction f nitrat to n trites are variable It is probably the same with haemolyti action so that the erection f ne species based on the characters is clearly unjustifiable Transf of olonies should be carried out every weeks but they can be kept ali e for a month by refrigeration which is best carried out on dextrose agar

Immunity Reaction

S far is know work carried out upon the cutaneou sensitivity of ctinomycotic pat nt and the presence of antibodie in the blood ha been performed with aerobic strain f *Act nomyce* They h e therefore no si ificanc in rel tion t d ease cau ed by *A israel*

Experimental Inoculation

Despit many ttempts no one ha y t succeeded n reproducing the haracteristi lesions f actinomycosis by jecting *Act nomyce israeli* int animals

Grootten (1934) by surgical introdu tion of fragments f Veillon agar bearing olonies f *A israel* int the abdomen of rabbit has noted the ppearance f clubbed granule

Emmons (1938) using strains of *A bov* (*israel*) of h man or bovine origin failed omplet ly However by repeating inoculation intra m scularly in the g nea pig Emmons ha been able to produc abscesses which lasted longer than in newly treated animals From the pus he reco ered actinomy otic granules de oid of cl bs

Rosebury Epps and Clark (1944) summarized their results s follow repeated inoculation with pure ultures f 9 strain of I israeli arously injected into 4 guinea pigs and 16 rabbits have mostly yielded negati

results However an experimental actinomycosis was obtained in animals evolutive and mortal in guinea pigs and one rabbit localized and benign in other rabbits Intravenous or intraperitoneal injections repeated with large amounts of *Actinomyces* appeared to be quite ineffective whereas single or repeated subcutaneous injections merely produced slow lesions from which the parasite could only rarely be isolated again Fatal reactions were sometimes observed after intrapleural injections or together with an inoculum of ground and sterilized salivary calculus Intracutaneous injections of living or sterile cultures in rabbits already inoculated and not so treated revealed quite clearly that an allergic condition is associated with a progressive infection Altogether the results obtained agree with the view that actinomycosis is an endogenous infection but show that the essential factors in the pathogenesis of this disease are as yet unknown

It is well to remember that the method of acidification of sputum as used in connexion with the inoculation of tubercular sputum in the guinea pig destroys *Actinomyces israeli*

Actinomycosis in Animals

Actinomycosis is known in a great many animals both wild and domesticated It has been noted especially frequently in cattle in certain regions In the United States according to Skinner Emmons and Tsuchiya (1949) actinomycosis is much more frequently found in abattoirs of the Middle West than in those of the South or the East but the difference they attribute to the poorer systematic study of the disease in certain regions The animals perhaps become contaminated with one another through the intermediate agency of fodder

As already indicated only a proportion of the symptoms of actinomycosis in cattle can be attributed to *A israeli* a great many are in fact caused by *Actinobacillus lignieresi*

Baudet (1934) produced an excellent study of the parasite causing actinomycosis in the dog better known as streptothricosis in dogs The pathogenic agent is near to or identical with *A israeli* and Baudet has suggested the name *Cohnistreptothrix canis* for it

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B. NOCARDIOSIS

Nocardiosis may be defined as a pulmonary disease, rare, usually fatal with a tendency to become generalized. It is caused by Nocardia [illegible]

The species of Nocardia [illegible] Actinomycetales which Waksman and Henrici (1943) placed in the family Nocardiaceae which includes the sole genus Nocardia. They are filamentous organisms, aerobic, in which the branching mycelium easily fragments. They do not form conidia. Gram [illegible] like the Actinomyces [illegible] are not acid fast but not alcohol resistant. Certain species [illegible] the [illegible] are [illegible] appear to be the only [illegible]

Nocardia asteroides (Eppinger) Blanchard 1896 [illegible] It is [illegible] species responsible for nocardiosis as defined above. It becomes pathogenic freely found in nature which occasion [illegible] named the following synonyms:

Conant and Rowbury (1948) [illegible] Actinomyces asteroides [illegible] Sartory, Meyer and Meyer 1930 [illegible]

Cladothrix asteroides Eppinger 1890 — Actinomyces [illegible] Baldacci 1939

Streptothrix carnea Rossi Doria 1891 and [illegible] informe Baldacci [illegible]

Streptothrix freeri Musgrave and Clegg 1907 — Actinomyces asteroides [illegible] color Baldacci 1939

Actinomyces gypsoides Henrici and Gardner 1921

The first case of nocardiosis was described in 1891 by Eppinger, found and isolated an aerobic *Actinomyces* Gram positive and acid in cerebral abscesses and meningeal exudates. Since then a number of cases (less than 100) have been described usually under name actinomycosis. Most cases were diagnosed at autopsy. The starting point is a pulmonary disease characterized by multiple abscesses pulmonary lesions are frequently complicated by cerebral lesions subcutaneous abscesses. According to Kirby and McNaught out cases the lungs were involved in 28 and in 10 there was cerebral metas... The abscesses were deeply seated as in the patient of Binford and (1945) or they were situated in the ischio rectal fossa.

Prognosis is very poor and the issue usually fatal (28 of the ... cases Kirby and McNaught). Further therapeutic measures were lacking very recently however the introduction of sulphamides without having given any striking result undoubtedly on account of generally being used too late *promise better for the future*.

In pus and sputum *N asteroides* is composed of branching filaments simply bacilliform Gram positive element. It does not form gran... The filaments and bacilliform components are equally acid fast ... demonstrated by the use of a modified Ziehl Neelsen technique. In... it is useless to employ an acid alcohol solution to demonstrate this ... fast property for the filaments and bacilli decolorize. Cholsworthy (1... recommends that after staining with warm carbol fuchsin for five min... destaining should be carried out with a 5 per cent sulphuric acid solu... for a limited period the filamentous forms in sputum withstand de... not longer than 5 minutes while in culture the filamentous form ... for 60 seconds and the bacilliform and cocciform element do not ... destaining beyond minutes. All the same Drake and Henrici (1... insist upon destaining with sulphuric acid alone i e lacking alc... Confusion of bacilliform element with Koch's bacillus is possible.

Nocardia asteroides may easily be cultured upon any medium suit... for aerobes at 37 C and at laboratory temperatures. Development how ver slow and several week are needed for the production of ... colonies. On agar the smooth colonies are soft *humid granul*... cerebroid and their colour progresses from yellow through orange t... On Czapek's medium where pigment develops most readily the colou... yellow or deep orange.

Experimental inoculation in the rabbit demonstrat the ... sensitivity to intravenous injection of *N asteroid* the anim ... a variable period usually rather short (days for Drake and Hen... [1943] *48 hours for Binford and Lane [194]* 28 days for Buch ... and Roux [1948]) exhibitin multiple absces of diam ter mm in organ. Subcutaneous or intramuscular injections in the rabbit or guinea pig ends in localized abscess formation at the inocul tion ... heal after suppuration. Peritoneal injection in the rabbit is pra... without result whereas in the guinea pig it is followed by fatal peritonit...

MYC F CAU FI BY A TINOMYOETE

According to Conant and Rosebury (1948) N. asteroides is the only Nocardia species pathogenic for laboratory animals.

Drake and Henrici (1943) prepared an asteroidin by evaporating broth cultures of N. asteroides killed by warming to one tenth of their volume. They have also studied in the rabbit and the guinea pig the allergic reactions caused by intratesticular inoculation of suspensions of N. asteroides in oil. After 30 days the animals showed a strong cutaneous reaction to an injection of crude unwarmed extract. The antigen is localized within the proteinaceous component of this extract.

There is no cross reaction with Koch's bacillus.

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6 TRICHOMYCOSIS

Trichomycosis or lepothrix is a disease of the axillary hair characterized by yellow red or black nodules caused by Nocardia tenuis and various micro organisms.

The synonym of the disease is trichomyceis completed. Although known since Paxton (1869) first described it, it received the name of lepothrix from Wilson while somewhat later it was called it Trichomycosis palmellina. Yet other appellations are met with in the literature as follows: Trichomycosis axillaris, Trichomycosis nodosa, Trichomycosis chromatica or Chromotrichomycosis and Trichomycosis nodosa, Trichomycosis.

Castellani (1911) first worked on the cause of trichomycosis and red and showed, recognized the three chief varieties yellow black and red and showed that the yellow variety is caused by an Actinomycete, Nocardia tenuis whilst the black and red varieties are caused by an association of N. tenuis with micro organisms producing black and red pigment respectively. These micro organisms are called respectively, Micrococcus nigrescens Castellani (1911) and M. cruoreus castellani M. crocococcus nigrescens.

Chalmers and O Farrel (1913) *Nocardia tenu* Castellani 1911 ha the following synonyms—

> *Discomyces tenui* Castellani 191
> *Cohnistreptothrix tenuis* Ota 1928
> *Actinomyces tenuis* Dodge 193)

Porcelli (101) is credited with the rather difficult achievement of obtaining cultures of N *tenui* It i how ver cl ar that Macfie obtained cultures at Accra before the Italian worker by the followin method scrapings from infected hairs are soaked in ab olute alcohol before bein transferred to ascitic agar After incubation for several days at 3° C small transparent colony composed of *fine and elongated mycelial fil* ments appears on the surface of the agar The olony grows slowly and remain translucent and almost invisible Sub culture upon a citie agar grow more quickly—within 4 hours—but never any larger Only the central regions of the colonies become opaque and re emble ground gl ss The strain is easily maintained upon ascitic agar all attempt to culture N *tenuis* upon ordinary agar have failed The non acid f st filament are either Gram positive or negative in the youn culture but become more strongly Gram positive in older ones

Micrococcus nigrescen which accompanies N *tenu* in the black form of the disease has been cultured by Castellani (1911) whil t Chalmers and O Farrel in 1913 isolated *M castellanii*

N tenuis cannot be inoculated into human hair s ... le

Trichomycosis shows a marked pref rence for attackin hair in tl axillary regions but instances have been recorded of hair of the pubic and inguino scrotal regions having been attacked (Chalmers and O Farrel) The black and red varieties are almost entirely trop al Howe r Castellani and Wilkinson (1923) ha e described some case f this di e in England Different varieties may be encountered on the same p rson The incubation period is unknown but is probably at lea t tw we k

Hair attacked by lepothrix xhibit either i lated nodule or a thick and irregular sheath Microscop cal examination sh ws the nodule or sheaths to be composed of very fine filament often reduced t b cilliform r coccerform element which pu h aside the ha r cuticle and d elop *beneath it le ving the hair itself intact* According to Porc lli the intra hair is penetrated by N *tenu s* but it may w ll be that this a sertion rest upon the study of poor preparation In th black nd r d form are found large black or red cocci besides the filament of N *te*

Macfie (1916) discovered that besides the three l sual forms th re is a fourth brown form (*var fusca*) which he described rather inadequ t l and from which he isolated a diplococcu associat d w th N *t* Again Ping Ting Huang (1933) i olated from ca es of lepothrix in J p n an *Actinomyce sendaie* i w th black ultures ompl t ly d ff rent from those of N *tenui*

Those subject to trichomy osis ft n ha axillary hyp rhydr It

is hard to decide whether this hyperhydrosis or the trichomycosis itself is the cause of the armpit erythema which sometimes appears.

Treatment of trichomycosis consists essentially of shaving off the hair in the attacked region together with powdering.

Diagnosis is simple and trichomycosis is not readily confused with the pediculosis.

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D ERYTHRASMA

This disease must be classed with those caused by Actinomycetes, though its causal agent is not known with certainty. It may provisionally be named Nocardia minutissima or Actinomyces minutissimus (Burchardt 1859) Verdun 1912. The synonymy of this organism is much muddled and the following names are retained—

Microsporum minutissimum Burchardt 1859	*Sporotrichum minutissimum* Saccardo 1886
Trichothecium ... Neumann	*Microsporoides minutissimum* Vuillemin ... Lemaire 1906
1885	*Discomyces minutissimus* ... Verdun 1907
Microsporum gracile Balzer 1881	*Oospora minutissima* Ridet 1911
Leptothrix ... Burzorero 1888	

This fungus has not however been cultured here though workers have claimed to have obtained cultures. Our own attempts like those of Sabouraud Plaut and many others have proved fruitless.

The organism was apparently first seen by Burchardt in 1859, the disease was called erythrasma by von Baerensprung (1862). Balzer is chiefly responsible for the confusion of its classification by the German school with that of *Pityriasis versicolor*.

Erythrasma characteristically produces spots of regular outline, delicately scaly, erythematous or pigmented and lacking any apparent tendency toward spontaneous healing in the central region. The pigmentation of the spots varies from café au lait as in *Pityriasis versicolor* to brown, a tinge which may become very deep. Usually well tolerated

and hardly even accompanied by an itch the erythrasma patches may when there is much loss of moisture produced by physical exercise or fever project and become slightly sore They never develop vesicles Erythrasma is mostly confined to the inguinal fold more rarely the axillary fold and occasionally the sub mammary fold In man it is especially found in the lower part of the left inguinal fold contact with the scrotal skin apparently favouring its development It is a disease of adults very common in men much less so in women and exceptional in children Gougerot considers that erythrasma attacks practically all men at some time or other On the other hand American authorities consider the disease to be much less frequent in the United States than in Europe It is not in evidence in the native Africans but it is very common amongst Europeans living in the tropics

From the clinical point of view diagnosis is rather easy but erythrasma must be carefully distinguished from the epidermomycoses especially *Hebra's eczema marginatum* and from *Pityriasis versicolor* When the scales of the inguinal or axillary regions fail to show branching and relatively large segmented filaments characteristic of dermatophytes erythrasma may be borne in mind The organism may be investigated by direct examination of the scales in chloral lactophenol or scales degreased in ether may be stained well in methylene blue and attached to a slide by collodion dissolved in a solution comprising parts absolute alcohol to 1 parts ether Observation must be carried out under oil immersion objectives for the organism is too minute for dry objectives It may present the appearance of short branching filaments of 1 μ maximum width or else of cocciform or bacilliform elements Attempts at culture scrapings on Sabouraud's medium always give negative result

Histologically erythrasma is characterised by slight hyperkeratosis and by minimum infiltration into the dermis

Treatment of erythrasma is usually considered to be easy but we do not hold this opinion Alleviation of symptoms is easily accomplished after the erythrasma has been irritated by perspiration and the friction accompanying the application of inert powders or 10 per cent boracic talc The use twice daily of 1 per cent iodized alcohol compresses moistened with a 20 per cent solution of sodium hyposulphite chrysarobin or anthralin may bring about a desquamation and apparent cure But in most cases a more or less rapid relapse sets in the presumption of cure is usually premature for the patient will not often continue to treat a patch of erythrasma which causes him no annoyance

CHAPTER II

Aspergillosis

THE name Aspergillosis is given to the [illegible] caused by Aspergillus species in man and animals. The most commonly isolated species is Aspergillus fumigatus. Aspergillosis is a well known disease of birds in captivity, especially aquatic species such as penguins; the question whether there is such a disease as human aspergillosis is a very controversial one, though a very rare form of the disease in humans may exist.

The Aspergilli, comprising about 300 species, form a very widely distributed group of Ascomycetes which live in the soil and upon organic materials. Together with *Penicillium* and *Mucor* species they are the most frequent contaminants of laboratories. Since sputum, ear wax and nails are exposed to the atmosphere, it is to be expected that Aspergillus species should appear upon them in abundance, and if one were not warned of the danger of analogy, one might feel justified in establishing a causality relation between a lesion which might appear and the fungus isolated from it. These risky conclusions find too easy support in certain developmental stages of lesions such as, for example, the greenish phase of certain onychomycoses attributed to *Aspergilli*. The correct conclusion is probably very different. *Aspergilli* are incapable of attacking a healthy nail but they are well able to develop in the breakdown products of nails attacked by a dermatophyte. The ease with which *Aspergillus* species grow in culture and their inhibitory power over many organisms result in the isolation of a saprophytic *Aspergillus* from the nail culture instead of the parasitic dermatophyte. This is no mere speculation, for since *Aspergilli* cannot attack keratin, a favourable nutrient medium is [illegible] for dermatophytes. Moreover, cases of so-called mixed infections involving an *Aspergillus* and a dermatophyte have been noted, Brereton and Warring (1946) reporting 13 cases of onychomycoses by *Aspergillus* indicated that in one case the infection was caused by an *Aspergillus* and *Trichophyton rubrum*. Without doubt the finger nails first attacked by *T. rubrum* were ultimately invaded by the *Aspergillus*. Another fact in support of those who favour aspergillosis is that injection of *Aspergillus* spores into laboratory animals often brings about a rapidly fatal condition. Even after eliminating those cases in which death of an animal is brought about by the injection of large doses of *Aspergillus* spores, there still remains the undoubted pathogenic power of a large number of Aspergilli for laboratory animals.

In human pathology it [illegible] from the first to reject all

aspergillosis di gnoses as eminently suspect and only t admit them with reluctance after all other pos ible cau es have been eliminated. *Even the classical cases of aspergillosis in pigeon fanciers and wig makers d not seem to be as convincing a formerly. In many pulmonary ailment Aspergilli and yeasts are secondary a ent of inf ction to which are t o often attributed a pathogenic power which they no longer poss.* Conant *et al* (194 p 198) commenting upon the ex f mining al *aspergillosis* reported by Iinck (1939) and also that of Jost (193-) concerning a cerebral abscess due to *A pergillus* wrote In both cas *mycelial filaments were pre ent in the le ions and the diagno is of asper gillosis* was extremely probabl but it was not demonstrated

If in man any diagnosis of aspergillo is must b su pe t in the majority of case this is not so for animals and especially bird in captivity These e pecially sea bird p ay a very he vy toll and ev ry *year many specimen are lost from the world zoolo ical gardens on* account of aspergillosi Ainsworth and Rewell r ntly (1949) con idered this question in an interesting article ba ed upon their observations in the Zoological Gardens at Re ent s Park London Aspergillosis in birds is eminently a disease of the respiratory system The air sacs e pecially the *anterior thoracic are the most frequently involved then come the lun* In only three of the 8 cases described by Ainsworth and Rewell the abdominal viscera were attack d

The lesion are nodule pre ent in the air sa es or granuloma which invade the lungs Asper illosis abo e all affect birds in captivity but *in some cases d ath so wiftly f llow capture of the bird that the pre* existence of the inf ction mu t be admitted Opinion to the etiolo y of aspergillo i i divided between two groups one maintaining th t aspergillo is is endemic among t wild bird and that capti ity bring it to a he d the other that a pergillosis i a con q nce of aptivity to which *ert in particularly susceptibl wild bird fall vi tim*

Whichever view be correct the di ease cannot be rre ted once it I tarted and death soon su pr ves No ff ctiv th rapeutic measures are known

Identification of *Aspergillus* peci s is difficult Thom and Ra er (194) should b n ulted on thi subject

Note One must al o ex rci e the great st ut on n cepting he m of mycose ause b y *Penicillium Mucor* nd *Cephalosporium* sp respectively ref rred to a Penicilliosis Mucormy s r Cephalospor (f Conant *et al* 194) The e fun are so wide pread in n ture and uch frequent laboratory contamin nts that no m n f n in be attached to their i olation n culture The truly p tho enic fun produce a cl ar precise and seldom al rant my t mat logy whil t the false p tho genic fungi h no prope ymptomatolo y

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J[illegible] (I.) *Aspergill[illegible]* [illegible] (19[illegible]) **24** [illegible]

L[illegible] (K.) [illegible] (19[illegible]) [illegible]

Th[illegible] (C.) & R[illegible] (K.) [illegible]

North American Blastomycosis or Gilchrist's Disease

Definition

North American blastomycosis or Gilchrist's disease is a mycosis caused by *Blastomyces dermatitidis* Gilchrist and Stokes 1898, characterized by warty cutaneous lesions and lesions of more deeply seated organs with a predominance of pulmonary lesions.

The designation blastomycosis is somewhat unfortunate, for it suggests the implication that the causal agent is a yeast, since the fungus involved exhibits a yeast-like morphology in certain stages of its development, whether parasitic or cultural. Further, it leads to confusion with so-called European blastomycosis, known also as cryptococcosis or torulosis, caused by a true yeast, *Torulopsis neoformans*. The eponym "Gilchrist's disease" is preferable and pays tribute to the worker who in 1894 described the first known case.

It is noteworthy that in the United States the disease has often been referred to as "Chicago disease" (though this tendency is diminishing) because of the large number of cases originally from Chicago. The impression may sometimes have been gained that "Chicago disease" was of different origin than Gilchrist's disease, but this is not actually the case.

Historical

In 1896 Gilchrist published his account of a case of dermatitis due to a blastomycete which he had observed in 1894. In 1898 with Stokes he described a further case of this disease under the name of "a case of common pseudo-lupus" and produced with his collaborator a description of the parasite. The first description of the parasite must thus be attributed to these two authors, whatever the name that it may ultimately receive and whatever the systematic position to which it may eventually be assigned.

Importance and Geographical Distribution

Gilchrist's disease is a comparatively rare malady, of which some 300 cases have been described, but only a hundred of these are unquestionably due to *B. dermatitidis*. In 1939 Martin and Smith showed that of 34[illegible] published cases only 90 (about 30 per cent) were authentic instances of

Gilchrist disease. It is a disease of old age found especially in poor farming populations. Men are more frequently attacked than women in the proportion of about 10 to 1 (statistically given as 8 to 1 or 9 to 1). All races are susceptible; black races have sometimes been thought to be less sensitive than white, but this is doubtful.

The geographical distribution of Gilchrist disease is strictly limited to the United States of America, especially the Mississippi Valley, California and Illinois. Its already noted frequent occurrence in the Chicago area has led to the name "Chicago disease".

Apart from the United States, certain cases have been recorded in England and Canada. Starrs and Klotz (1949) in a recent analysis of Canadian cases have, however, noted that practically none of the cases reported for Canada could be established without doubt as Gilchrist disease, and further their personal contribution of a new case is inconclusive since no culture of the parasite could be made. In 1946 Brody reported an undoubted case (histopathology and culture) of North American blastomycosis which unexpectedly appeared upon an American soldier during his stay in France. The writer rejected the possibility of the disease having been contracted in America or England since the generally accepted incubation period (1 week to 4 months) was much shorter than the time which had elapsed before the appearance of the symptoms (20 months) in that particular case. According to Brody there remained the possibility of contamination from a parcel sent from the United States.

Numerous cases of blastomycosis have been claimed in many countries besides America. They are usually accompanied by mycological or even anatomopathological reports too incomplete to permit of classification and it seems appropriate to conclude that Gilchrist disease is almost certainly endemic to the United States.

Etiology

There is as yet no precise knowledge of the exact origin of the pathogenic fungus and although certain writers have considered themselves able to report that *B. dermatitidis* is widespread in nature, this is difficult to prove. In 1914 Stober isolated from rotten wood found in the dwelling of one of his patients suffering from blastomycosis a mould similar to *B. dermatitidis*, from which he prepared a vaccine to which a patient reacted sharply. Of even greater interest are the observations of De Lamater (1948) who having isolated *B. dermatitidis* at various times from the urine of a patient with prostate trouble considered that urine may be a source of contamination of the soil. Following this up he inoculated sterilised soil with cultures of various strains of *B. dermatitidis* and obtained good growths of the mycelial form of the fungus. Unfortunately so far as we know the results obtained by this worker have been reported only in a very short note published on the occasion of a reunion; one would wish for more detail.

Instance of conta ion betw n man and man or do and man has been noted but they are exceptional

Pathogenic Agent

At the present time it seems unnecessary t attribute Gilchrist d to any agent other than *Blastomyces dermatitidis* Gilchrist and Stokes 1898 However many attempts have been made to di tingui h diff rent pecies or varieties from amon t the i olated strain but it may well be that the various morphological forms are only variations f the ame species On the other hand although mo t authorities agree upon retaining for the fungus in question the name whi h wa given by tho who first studied it many synonyms are to be found in the literature f which the followin are the commonest—

Oidium dermatitidis Rickett 1901
Cryptococcus gilchristi Vuillemin 190
Zymonema gilchristi Beurmann and Gougerot 1909
Cryptococcus dermatitidis Brumpt 1910
Mycoderma dermatitidis Brumpt 19
Glenospora gammeli Pollacci and Nannizzi 1927
Blastomycoides dermatitidis Castellani 1928
Blastomycoides tulanensis Castellani 1928
Endomyces capsulatus Dodge and Ayers 1929
Geotrichum dermatitidis Brygal 1931
Monosporium tulanense Agostini 193
Glenospora brevis Castellani 1931
Endomyces capsulatus Moore 1933
Endomyces dermatitidis Moore 1933
Zymonema dermatitidis Dodge 193
Gilchristia dermatitidis Redaelli and Ciferri 1934
Torulopsis dermatitidis Almeida 1933
Zymonema capsulatum Dodge 193

In tissues *Blastomyces dermatitidis* appears as a large rounded cell 8–15 μ and sometimes 1– μ in diameter with a rather thick wall which gives it the appearance of double contour Certain of the cells appear to be budding The bud which is usually smaller has a very l g and a much finer membrane than the moth r cell Oc ionally n t a l f forming a separate bud tl ll long at and l k n a form re ent f a hand mirror More exceptionally a whole row f rounded cells is to be found arranged in a row before their separation fr m one another These cells can easily be distingui hed fr m tho f *C nt la all c* th latter being much smaller and often ated with my lial fil nt The cell of *Torula neoformans* are surrounded by a gel fr th very thick within the t sue ltl u h tl mem brane f *B* may be somewhat thick it n true ap ule Conf th *Bl myces* is most lik ly the ron l budding whi h char acterizes this pecies should l look l for *Coccid* k ndospore whi h are n r found in the ll f *Bl*

Cultures of *B dermatitidis* are of two kind On blood medium at 37 C the colonies are yellowish whit waxy of soft consistency and cerebriform in form The colonies at C or 30 C form a downy mould which at first but now and then brownish Smooth colonies recovered from coremia and others of floury appearance have been described

The colonies cultured at 37 C represent the yeast like phase corresponding to that within the tissues Here are to be found the large rounded and budding cells The buds have a very large base which readily distinguishes them from true yeast The outlines of mycelial filaments may also be found in this phase

In colonies grown at C or 30 C some yeast like elements may be found but the mycelial phase predominates The mycelial filaments are not however so fully developed as in the first subcultures for the primary cultures represent an intermediate condition between the yeast like and the mycelial phases In the first subcultures are found mycelial filaments which segment and branch and often coremia Upon these mycelial filaments are borne the conidia either directly or by intermediary conidiophores 1-10 μ long The conidia have smooth walls and their abundance and dimension vary considerably with the strain They are round oval or pyriform with diameters 3- μ In old cultures chlamydospores 7 18 μ may appear with thick and irregular walls

Temperature is the essential factor which determines whether the yeast like or the mycelial phase shall appear Raising the temperature up towards 33 C under laboratory conditions always gives the mycelial phase above 33 C from 3 -37 C the yeast like phase is obtained and lowering this temperature results in the reappearance of the mycelial phase One or the other of these phases may thus be obtained without difficulty and it is unnecessary to use complicated techniques or to pass again through an animal as is the case with *Histoplasma capsulatum* or *H farciminosum* However like *H capsulatum B dermatitidis* prefers solid media for its yeast like phase and it is only with extreme difficulty that it develops this phase in liquid media The optimum pH is more on the acid side for the mycelial phase (pH 5-7) than for the yeast like phase (pH 6 5-8 5)

Levine and Ordal (1946) obtained excellent growth of *B dermatitidis* upon glucose peptone media but they noted that the growth was slower if one used an inoculum made up of an emulsion of spores from the mycelial phase than one made up from the yeastlike phase Further on glucose media containing various salts and especially ammonium sulphate as the nitrogen source only the inoculum made up from the yeast like phase developed appreciably

Symptomatology

Blastomyces dermatitidis probably has two means of access to humans The one is cutaneous leading to localized and somewhat benign symptomatology The other is respiratory leading to the severe generalized form (systemic blastomycosis of American authors) with lung damage in most

1964. The generalized form of blastomyco is can equally give rise t cutaneous lesions but as noted by Starrs and Klotz (1948) whereas in the primary cutaneous form the lesions are restricted to the expo ed parts of the skin in the generalized form they are confined to the covered regions Both forms will be dealt with in succession

As already indicated the cutaneous lesions in the *primary cutaneous* form appear upon uncovered or expo ed parts face hands wrist feet and ankle joint The primary lesion i a pimple (papula) which lowly spreads at the periphery and becomes covered with a scab bearing a sanious pus The edges of the spreading papuls describe a perfect circl or are serpiginous The centre tends to heal in step with the pread of the lesion leaving an unpleasant scar A typical f ature of the margins i the enclosure of many small abscesses in which the parasite i easily d tected From these may be obtained material of the pure cutaneous form for purposes of culture Wartiness is also typical of the lesion margins

In the *generali ed form* pulmonary lesions occur in 9 per cent of the cases cutaneous lesions in 50 per cent bony lesions in 60 per cent (especially ribs and vertebra) damage to liver spleen and kidneys in 40 per cent and prostatic lesions in 20 per cent of patient Lesions of the central nervous system occur in about 30 per cent of the case

Pulmonary lesions are usually the first sign of a generalized blast mycosis accompanied by cough soreness blood streaked sputum and rather high fever As the pulmonary symptom spread the di ea is disseminated to other organs notably with the formation of subcutaneous abscesses These appear as nodules or gummy masses which soften open and discharge The margins of the ulcer thu formed are warty and enclose many small abscesses as in the primary cutaneou form

Histopathology

Study of a cutaneous biopsy reveals two very special f atur The first involves considerable epidermal hyperplasy whic may cause the lesion to be taken for an epithelioma The second i the pr ence f minut abscesses in the epidermal or dermal layers In the e micro al c se are found cells of *B dermatitidis* liberated in the pus or encl ed in macrophages

In other tissues the histological reaction i that of a granuloma leading to necrosis and suppuration In the lungs are found a great many miliary abscesses comprising cells of *B dermat tidi* multinuclear and giant cells plasmocytes epithelioidal cell and occasional eosinophils

Blastomycetin

Patient with North American bl stomycosis are likely t r t bl t mycetin introduced intradermally by the formation of an rythem tou papula which forms three or four days after the injection and may in ery allergic patients be accompanied by a low abscess formation t the place of inoculation When this reaction is positiv it is t be con luded th t

the patient ha bl1 tomyco is nd j ogno is is f ourilk A negati reaction does not howev r indicat freedom from bl stomyeosis and f it is known from another techn que that the patient ha Gilchrist disease the prognosis is not fa ourable It would seem that the con clusions t be drawn from this procedure are similar to those which the leprosy specialist draw from Mitsuda s reaction in Hansen disease

According t Jones and M rtin (1941) the intracutaneous test technique is a follows the cutaneo tests are arried ut by a heat killed accine prepared by suspending in sterile physiological saline the y ast like phase of a culture of *B dermatit d* on blood agar at 37 C This suspension is c ntrifuged in a H pkins tube and the sediment is onc more suspended in enough physiological saline for a dilution of 1 1 000 by lume The standard suspension is warmed for four hours at 60 C It sterility is confirmed by inoculatin copiously upon a tube of blood agar which is maintained at 37 C for at least ten day A an antiseptic 0 3 per cent tricresol is added and 0 1 ml of this suspension is injected intradermally to te t the skin Durin th following 15 or 20 minutes an erythematous zone usually appears t the level of the injection This react on has no specific alue and occurs in patient with other typ of pulmonary disease The characteristic reaction commences 1 -24 hours after injection and reaches a maxim m in -4 days It exactly resembles a posit ve tuberculin re ction In very aller ic patients a sterile abscess may appear t the point of inoculation The appearance of a posit e reaction may be consid red an indication of blastomycosis This diagnosis is erified by the presence of ant bodies in the patient s serum

Demonstration f complement fixation is obtained by using anti en a su pension from a living culture of the yea t like phase obtained by growing on blood agar at 37 C The titre f this suspension is determined xperimentally The proof of complement fi tion in blastomycosis has pecifi alue when it is positive When negati it has no diagnostic significance but indicates in the case of sufferer from Gilchrist s disease a certain resi tance of the organism It is to be noted that this reaction is alw y negati in primary cutaneou form

Result of these two reactions are bviou ly essential before considering therapeutic mea ures as their study plays an important role in tre tment

Treatment

Gilchrist dise se is one of the rare serious myco which can be cured it is sensiti to potassium iodide which may therefore be applied in the most appropriat dose specifi therapeutic measure

Before administerin potassium iodide it is nece sary to find out the patient sensitivity or more precisely his allergic condition A cutaneous test is carried out by injection of killed ccine s already described If the observed cutaneous rea tion 4–48 hours fter injection does not exceed 1 cm in diameter potas ium iodide may be administered by a rapid method scheduled by Conant *et l* as follow a saturated solution

of potassium iodide is administered at the rate of 3 times 3 drops per day and increased by 3 times 1 drop per day until the patient receives 3 times 100 drops per day. Having reached this dose a fresh beginning is made *from 3 times 3 drops per day*.

If the patient's reaction from intradermal injection of vaccine had a diameter greater than 1 cm the patient must be desensitized by progressive injections of killed vaccine before administering potassium iodide. This desensitization is carried out by subcutaneous injection every other day *of 0.1–0.3 to 1 ml* of vaccine diluted to 1 : 100 if the reaction is 1 cm, 1 : 1,000 if the reaction is 3 cm and 1 : 10,000 *for a reaction exceeding 3 cm*. Often after two weeks a sufficiently satisfactory desensitization is obtained to permit commencement of the potassium iodide treatment. In this case a slow method is employed, consisting of administering a saturated solution of potassium iodide at the rate of 3 times 3 drops per day and increasing by 1 drop per day (not by 3 times 1 drop) until the dose 3 times 40 drops has been reached, after which one reverts to the initial dose.

Vaccine injection may reveal a local or a general reaction accompanied by temperature rise. In these cases the commencing dose should be lower.

Iodine has also been introduced as sodium iodide injected intravenously (1 g per day) or by the inhalation of ethyl iodide. In the cutaneous form X-rays often produce very useful results.

It is obvious that a symptomatic therapy will accompany a specific therapy.

Prognosis

Prognosis of North American blastomycosis differs according to whether the type in question is cutaneous or general. Whilst it is favourable in the former, it is customarily fatal in 90 per cent (Martin and Smith) of cases of the generalized form. As already indicated, a high antibody production is an unfavourable sign, whilst a violent cutaneous reaction is the most hopeful. Death occurs from 2–3 years after the appearance of the first clinical signs.

Differential Diagnosis

It is of little value to enumerate the series of diseases with which blastomycosis may be confused in the generalized form. The cutaneous form may simulate warty tuberculosis, chromoblastomycosis, inguinal granuloma, syphilis and a great many other ulcerous conditions.

Mycological Diagnosis

The mycological diagnosis of blastomycosis is established by seeking the parasite in the pus or in sections and by culture.

Animal inoculation, as will presently be indicated, is of little value.

Investigation of the parasite in the pus is made by direct examination

without the addition f a clearing ag nt or possibly bett r after dil tion of the pus with a drop of 20–30 per cent caustic potash If budding form are not found mmediately it may pro useful t raise the coverslip and re xamine 4 hours later

Sections of t sues may be stained by eo in haematoxylin but according t d Aunoy and Be en (1 30) superior result may be obtained by a sil er impre nation method

Cultur may be initiated from pus g thered from micro abscess c putum and urine The suspected material is cultured upon blood aga nd incubated at 37 C or on Sabouraud medium t laboratory tempera ture Cultur t be must be retained for r 3 weeks before being dis carded

Experimental Inoculation

As already me tioned t is difficult to inoculat bla tomycosis in animals o this method is not recommended in est blishing a diagnosis It may be resorted to however t confirm the pathogenic nature and to retriev a o the budding f rm f strain of *Blastomyces dermatit I* already isolated in culture

The mo t suscept ble animal is the white mouse subject d to intr peritoneal inoculation The g inea pig t relati ly insusceptible nd the rabbit almost ompletely so For successf l inoculation it is necessary t n e large quantity of spores In the whit mouse it is possibl to w tch the ppearan of granulations on the peritoneum from which buddin form f *B dermat tid* may be recovered

Blastomycosis in Animals

Benbrook Bryant and Saund rs (1948) in a recent re iew of animal ses erified that 11 cases ha been reported for the dog In this animal the pulmonary lesion s dominant but K lner has reported a case of cutaneous blastomycosis in a do which infected two members f th family with which t li ed Benbrook *et al* reported a case of blast mycosis in mare the diagnosis unfortunat ly was ba ed only histopatholo ical examination

Taxonomy

The haracters of *Blastomyces dermatiti I* s ha ing been pre c ted it is perhaps better to refrain from settin forth a tentat e systemati scheme for parasite for which it is acknowledged by all that the binomial which designates it has no merit other than that of priority

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CHAPTER IV

South American Blastomycosis or Lutz's Disease

Definition

This mycosis is characterized by granulomatous lesions attacking the mucous membranes, the skin, the ganglia, the gastro intestinal tract and the lungs. It is called by *Blastomyces brasiliensis*. The nomen laturn of this disease is rather ill established. North American workers naturally call it South American blastomycosis in contrast with Gilchrist's disease which is North American blastomycosis. South American authorities prefer the name Lutz's disease in honour of the worker who described the first cases. The eponym Lutz Splendore Almeida disease is also widely encountered in which Lutz's name is connected with that of Splendore who was the first to cultivate the pathogenic fungus and also that of Almeida who made the first comprehensive study of the disease. Another name which is going out of fashion is that of paracoccidioidal granuloma, an appellation given at a period when a parallel had been established between Lutz's disease and coccidioidomycosis.

Evidently the name Lutz's disease ought to be retained in preference to that of South American blastomycosis since the latter name gives undue prominence to the yeast like phase which the parasite undergoes in the tissues.

Other synonyms are found in the literature particularly—

Brazilian blastomycosis	Paracoccidioidal granulomatosis
Malignant coccidioidal lymph granulomatosis	Neotropical blastomycosial granulomatosis
Coccidioidal lymphogranuloma	Paracoccidioidosis
Malignant ganglionary granuloma of blastomycetic origin	Lutz's mycosis

Historical

Lutz (1908) described the first two cases. He recognized the characters which distinguish the causal agent of South American blastomycosis from those of coccidioidomycosis and Gilchrist's disease respectively, but he considered the differences to be slight. Consequently he put the three diseases together under the common appellation American hyphoblastomycoses.

Splendore (1909) described new cases of the disease and three years

later named the fungus responsible *Zymonema brasiliense*. Up to the present he has cultured it and inoculated it into several laboratory animals. Curiously enough since 191 Splendore has observed perfectly the multiple budding typical of the parasite in the tissues a character regarded as specifically diagnostic by modern workers. In spite of this during the ensuing years the question remained unresolved and Lutz disease is regularly confused with coccidioidomycosis. It was not until 19— that comparative study by Souza Campos and Almeida of the fungi responsible for the two diseases permitted them to be distinguished one from another. A little later Almeida proposed the genus *Paracoccidioides* in which he placed the agent of Lutz disease under the binomial *Paracoccidioides brasiliensis*.

In 1940 Conant and Howell established a correct parallelism between the agents of Gilchrist and Lutz's diseases respectively: they gave the name *Blastomyces brasiliensis* to the agent of South American blastomycosis.

Importance and Geographical Distribution

Lutz disease is a relatively frequent mycosis. Almeida has called attention to 500 cases in South America. According to Vergani and Bigliolo (1948) a thousand cases have been reported from Brazil.

The geographical distribution of this disease is essentially South American and especially Brazilian. In Argentina a good many cases have been reported. Some have been recognized in Paraguay, Peru and Uruguay. Apart from South America some rare cases have been discovered in Costa Rica.

The disease is found especially in young adults aged 30–40 with an allegedly great predominance of men to women (about 9 to 1).

All races are susceptible and the disease takes a heavy toll of manual workers in fields and on farms.

Etiology

Nothing is known of the origin of Lutz disease except that it seems to have a preference for land workers.

Pathogenic Agent

There appears to be only one pathogenic agent of this disease although several species have been described. The causal agent, *Blastomyces brasiliensis* (Splendore 191) Conant and Howell 194 . It is known under many synonyms, especially—

Zymonema brasiliense Splendore 191
Paracoccidioides brasiliensis Almeida 193_
Paracoccidioides cerebriformis Moore 193
Paracoccidioides ... Moore 193

In tissue the organism takes the form of rounded cells with double contour 10–60 μ in diameter which reproduce by single or multiple

budding. All agree that the form with multiple budding, which may be somewhat difficult to demonstrate in tissues, is the only form diagnostic of the species. South American workers have dubbed it the "wagon wheel (*rueda de timone*)" or "aeroplane motor (*motore de aeroplano*)" form.

Baghola (194) has produced a well documented work upon forms of *B. brasiliensis* in tissue and upon budding. The rounded cells in tissues are either free or enclosed within giant cells. Budding may commence in larger cells up to 40 μ in diameter. The buds, single or multiple, are of variable size with diameter 0.5-4 μ according to the size of the cell from which they are derived.

According to Baghola, besides most of those who have studied the matter, the effect is true budding and not a passage to the exterior of spores formed within the cell (cryptoporulation of C f rri and Pedaelli or endogenous sporulation of Fonseca). In certain mother cells Baghola has observed chromatin masses disposed around the periphery of the cell where they had been pushed by the formation of a central vacuole penetrating into pockets formed by a thinning of the wall of the mother cell and giving rise to the bud after having been surrounded by a little cytoplasm. There is no the formation of little channels such as has been claimed to be due to the elimination of buds formed inside the cell.

Cells with multiple buds are not encountered with equal frequency in all tissues. They are most readily detected in lesions with no outlet, pus, sputum, dropsical fluid, testicular fluid and pus from guinea pig testicle scarcely ever contain any.

Cultures of *Blastomyces brasiliensis* exhibit two phases according to the incubation temperature. Whereas at laboratory temperature filamentous colonies are obtained, at 37 C the colonies are made up of yeast-like elements similar to those recovered from tissues. As noted by Conant and Howell (194) these facts emphasize the similarity between *B. brasiliensis* and *B. dermatitidis*.

The *yeast-like phase* develops at 37 C on the usual media, addition of blood to the culture medium not being necessary. The colonies are glabrous, cerebriform and strongly resemble yeast colonies. As already stated they contain elements of identical morphology with those of cells present in tissues. The buds are either single or multiple.

The *filamentous phase* grows slowly (sometimes four weeks are needed for primary culture) at laboratory temperature or at C. The colonies are ... membranous or corrugated and covered at the centre with whitish down which tends to brown upon ageing. The branched and segmented filaments produce oval or round conidia similar to those found in colonies of *B. dermatitidis*. However, the conidial forms of *B. dermatitidis* are less regular than those of *B. brasiliensis*.

Transition from one phase to the other is easily brought about by making a fresh inoculation from a colony of any phase whatever and ... the temperature necessary for the phase required.

Symptomatology

Lutz s di ease takes two form localized and generalized or mixed

1 In the localized type the lesi n are cutaneo muco al lymphangitic or visceral The cutaneo muco al le i n are localized in the buccal mucosa (tongue cheek pharynx larynx palate) and extend toward the exterior encroaching upon the kin of the face The le ions of the buccal cavity commence with a small papule which ulcerate and spread from the margins The regional lymph nodes are rapidly invade l The cutane ous lesions are warty papillomatous and ulcerate at the middle with marginal hypertrophy The localized ganglionary lesions encroach upon the lymph nodes of the neck and produce a clini al picture trongly reminiscent of Hodgkin di ease The e lymph node may necro and drain to the ext rior through sinuses The visceral localization are most frequently met with in the caecal and appendicular region

In the mixed or g neralized type are encountered bucco lymphan gitic bucco cutaneo lymphangitic and cutaneo lymphangitic ymptom *associated with crippling of the gastro int stin l tra t and accomp ine l by* hepatome aly splenome aly a cites According to V rsiani (1918) more than per cent of case may l f und bony lesions involving destruction of th epiphyse and the metaphyses The frequency of pulmonary lesion in the mixed forms is still very controversial The Sao Paulo school consid rs this type of localization to l rare but this view i obviously being modified if reliance is pla ed upon the report of the 194 Conf rence on Lutz disease The Rio de Janeiro authoritie think on the contrary that lung involv ment i very frequent and occurs in a *many as 80 p r cent of the cases* Fialho (autopsi) found pulm nary lesions in 84 per cent of the case and in another serie of l ca btained them in 16 in tance (94 1 per cent) Nino (Argentina) re ard lung attack as inevitabl X ray reveal peri hilar and mediastinal no lule Sputum i purulent and blood streaked Ritter h recently (1948) reported two ases of tumour one cerebral the other cerebell r use l by *B bra lien* l ut apparently the organism wa not cultured

In the localized form the g neral ondition i w ll maint ined l ok ng the loc lization of l sion (bucco pharyng al f rm) l not pr tl ing stion f nutriment In the g neralized form f r is ontinu l reachin a peak in the v ning nd often xce l 39 C There i on siderabl ema iation and l o hypochromatou anæmi

Histopathology

Histolo i lly the le ions are nti lly imilar t tl met th Gilchrist s di e nd coc idioidomy osis consistin f gran l m rich in giant cell from which the pathog ni fungi n l re o red in gr t numbers Th re i n infiltrat on of the t u by lympho yt pl m st and lymphocyt polymo lear ne trophil nd eo in phil n men

rarely f nd At lit stag ne ro t n p lynuck ir c lls are more abun lant

Treatment

M ch progress ha re lt d from the introd ction of sulphonamide therapy by the South Ameri an work rs In fa t only the sulphonamid are eff cti It is not yet pro ed that their use results final cure but t is quit ertain that they pre t th spread of the disea e from the primary foci and heck the de elopment of the secondary foci especi lly the pulmonary lesions

Sulphapyridine may be administ red a an initial do e f 100 mg/kg f llowed by a do e of 1 g repeated ev ry fou hours so long a the dru may be taken satisfactorily

Patilha Gonçalves estimat that the blood concentration of sulpha merazine and sulphadiazine must to be act e rea h mg per ent whilst that of sulph thiazol m y be slightly le

I una Caset and Abb tt (1947) ppear t ha cured a patient suff ring from a b ceo l ring pulmonary form by the administration of sulph merazine at the rate f 3 g during the first day then g up t a tot l dose of 237 g

Potassium iodide h also been much used specially by Almeid Its therapeuti action is how er l and tl re ppears t be reil d in of dissemin t on if it is used

As to accines too f w results are y t ail ble for ny pprai l of their value

Prognosis

In general up to the introd tion f sulphonamide ther py progno is ha hitherto been regarded fatal after n terval wh h does not ppear t ha been definitely ascertained

In sp te of the very f vourable opinions f those who h v used th sulphonamides in Luta disease it still remains t be est blished th t they effect cure rather th that they simply rrest the dise

Differential Diagnosis

There are arious pos ble diagnoses accordin to the form whi h the disease may assume The lymphangiti form may often be conf ed w th Hodgkin disease Pulmonary lesions may be taken for t berculou taneous lesions for y w syphilis or South American leishmaniasi The haemorrhages from intestinal lesions may be onfused w th tho hara teristi of other dise ses in wh h blood is present in the stool

There may be confusion with other mycose such h topl m C l hrit disease and occidioidomyco is

Mycological Diagnosis

Specific diagnosis may b established in thre way

1 *Exam nation of the Orga m* The f ngus responsible for Lutz

disease may be looked for in secretion abscesses, sinuses and pus. Pathological material obtained from a swab or by tapping with syringe may be smeared out on a slide in a small quantity of caustic potash (30 per cent) and examined under a cover slip. It will be recalled that the yeast-like elements which have a diameter as much as 60 μ may produce one or more buds from 2–10 μ. Only the presence of the multiple budding forms confirms the diagnosis of Lutz's disease, since budding forms with single buds are also *found in Gilchrist's disease*. Non-budding forms will be distinguished from *Coccidioides immitis* by the presence of endospores in the latter organism. Certain forms of *C. immitis*, however, do not form endospores.

The pathogen may also be demonstrated in sections stained with eosin haematoxylin, May-Grunwald-Giemsa, or by one of the silver impregnation methods.

Culture Methods. Secretions, pus or biopsy scrapings are cultured on Sabouraud's medium and kept at 25° C or 37° C. The culture tubes must be retained for at least four weeks, as the fungus grows very slowly in the primary cultures.

3. *Animal Inoculation.* This should be carried out by one of the techniques indicated under experimental inoculation.

In conclusion, before a diagnosis of *Blastomyces brasiliensis* may be allowed, there must be evidence of forms with multiple budding in the pathological product, in culture kept at 37° C and in the tissue of inoculated animal.

Immunity

There is no specific reaction in Lutz's disease. Complement fixation studies starting with cultural filtrates as antigen have given positive reactions not only for Lutz's disease but also for sporotrichosis, chromoblastomycosis and with the serum of patients affected with dermatophytic mycoses (Almeida).

On the other hand, the intradermal injection of antigens obtained from culture is followed by swelling, erythema and occasionally discomfort. It is not certain whether this reaction is specific. The intradermal injection of coccidioidin produces no reaction, but blastomycetin (*obtained from cultures of B. dermatitidis*) may give a positive reaction.

Neves da Silva has recently prepared an antigen by sprinkling pus obtained from guinea pig testicle inoculated with *B. brasiliensis* for one hour at 56° C upon three consecutive days (tyndallization). Before the tyndallization process the pus, which is rich in budding cells, is diluted fifteen times with physiological saline. Intradermal injection of 0.1 c.c. of this suspension produces in patients with Lutz's disease an erythematous papule which lasts three days and tends to necrose in certain cases. The reaction is negative in controls or in those with other mycoses.

Experimental Inoculation

Inoculations may l mad either with pathologi cal product or with cultures but are usually carried out with the l tter Unfortunately most workers fail to indicat whether they ha e used the yeast like or the filamentous pha both forms are p thogenic

Both g inea pig nd mice ha been used satisf ctorily

1 In the guine pig inoculation mu t be carried out in the testicle Cult ral lement are recov red 48 hours after inoculation then they appears at first a n orch tis accompanied exceptionally (4 t mes out of 4 guinea pig inoculated according to Fialho and Gonçalves) by invol ment of the regional lymph nodes which however lways heal though it may be possible t recover the parasite from them The orchitic stage is followed by a softening phase which is complete w thin a month of inoculation by this t me the testicle is transformed t a sa of pus in which are present large numbers of budding form According to most observer however forms xhibiting multiple budding are here found but rarely anish nd return in tissue form by the sixth day Clinically the lesion

2 In mic ntraperitoneal jection is necessary Infe tion progres es slowly and 5 or 6 week after inoculation there may be detected small nod les containing budding forms in the mesent ry and other organs Neither of the animal species ha shown generalized inf ction

Taxonomy

The genus *Paracocci loide* has been erected on ccount of the alleged resemblanc between the pathogenic agent of coccidioidomycosis *C* *im tis* and that of Lutz s di ea In fact the presence of endospores in the tissue forms of *C* *imm t* and the exi tence of this fungus in unique cult ral form conclusi ly separates t from *Blastomyces bra l ensis* On the contrary *B bra il ensi* h strong affinities with *B dermat tid* like the latter it reproduces in the tissues by budding is dev oid of endo spores nd ha tw phases in culture depending upon temperature The only distingui hing feature is the occurrence of mult ple budding n the tissue form or the east like phase in cultures of *B bra liensi*

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CHELOID BLASTOMYCOSIS OR LOBO S DISEASE

This little known disease wa first described in 1933 at Recife m the State of Pernambuco by Lobo A second ca e wa disco ered at Rio de Janeiro in 1937 by Fialho by Area Leao Cury Mello and Ma ao Coto again in 1946 whilst Area Leao Coto and Cury in 1948 wrote interestin papers on the organism responsible for the dise e Fon c a and Are Leao have since 1940 assigned it to the g nu *Glenosporella* Nannizzi 1930 calling it *Glenosporella loboi*

Cheloid blastomycosis i an c ntially chronic di ase hara t riz l by the maintenance of a good general condition and the formation in the skin of cheloid papules in which are found great numbers f round l lls from 8–10 μ in diameter which reproduce by ne or by two bud

At ordinary temperatures the fungus grow lowly t form wh t nd slightly d wny colonies The fil ment are branch d and segme t l After being cultured for one or two months they giv ri to g neus or pleurogenous conidia which measure 1 by 8 μ or 3 by 10 μ Cult re kept at 37 C yield a yea t like phase which repr luce by ne r se ral bud

Inoculation into guinea pig testicle or mou peritone m lead t an orchitis which gi es way to suppuration From the pus may I re red the same forms ccur in human tissue

There are such e ident affinitie with *Bla tomyc I rasilie* and *B d rmatitidis* that if the cre tion of a new spe ie is justifi l it sh ll be named *Blastomyces loboi* rather th n *Gl nospor lla l boi*

Ap rt from their diff rences a pathogens these three sp cies may be distingui hed from one another follows budding single in *B dermat tid* single or double in *B lobo* and single or mult ple in *B brasilien is*

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CHAPTER V

The Cephalosporioses

UNDER THE NAME are included [illegible] produced by Imperfect Fungi of the genus *Cephalosporium* Corda, of which the type species is *Cephalosporium acremonium* Corda 1839. This saprophytic species (from soil, decomposing plant remains, dead insects) has repeatedly been isolated from different types of lesions, and it is doubtful whether it is really pathogenic or not for man. A fair number of *Cephalosporium* species are pathogenic for plants and certain arthropods.

The genus *Cephalosporium* typically has a vegetative mycelium made up of segmented hyphae which bear sporophores inserted at right angles upon which develop a mass of terminal spores, oval or cylindrical in shape, bound together by mucilage. These conidia are the myxospores. The genus is distinguished from *Acremonium* Link 1809 in which the sporophores usually bear at their extremities one fusiform spore which is easily detached.

Cephalosporium species have been isolated from epidermal lesions, inflammatory or otherwise (intertrigo, onyxis, vesiculose conditions), from mucous membranes (buccal, ocular, vesical), from blood and sputum.

The multiplication of lesions together with the ubiquity of *Cephalosporium* species renders very suspect the already numerous works which attribute the production of a variety of lesions to various species of *Cephalosporium*. The well documented work of Coutelen, Cochet and Biguet ("Les Cephalosporioses humaines," *Ann. Parasit. Hum.* (1948) 23, 5–6, 304–98) may profitably be consulted on this matter.

CHAPTER VI

Chromoblastomycosis

Definition

Chromobl stomycosis is a chroni dermatosis caused by the accidental injection of various species of Fungi Imperfecti belonging to the genus *Phialophora* C nerally confined t one of the lower limbs it is char cterized by warty nod le which develop slowly into a vast papillomatou sheet and end w th or without ulceration This infection disease is not contagious

The d ease w first described under the name erracose dermatitis (Lane 191 Medlar 191) The term chromoblastomycosis was proposed in 19__ by Terra Torres da Fonseca and de Area Leao In spit of numer ous criticisms this term is the most frequently used t present The most important of these criticisms wa that the word suggested a mycosis c used by budding fungus Th m 193 led Moore and de Almeida to propose the word chromomycosis which was used in the first edition of this Precis but which does not seem to hav become popular Other names such a erruceous chromomycotic dermat tis (Redaelli and Ciferri 194_) and disease of Lane Pedroso Gomez (Pereira Filho 1949) hav met with little appro al It would seem that the denomination chromobl stomy cosis without having priority is so old and well est blished that it modification or replacement would lead to unnecessary confusion This term only is used here

Historical

The first case of hromoblastomycosis w dia_nosed in Boston in 1915 by Lane and Medlar These workers published their observation separately the former dealing with the linical aspe ts and the latter w th the haracters f the fungus whi h he had olated and described F ye rs later Pedroso and Gomez (1920) a_ain finding the disease in Brazil ttributed it to an organism identical w th the one olated by the North American workers and Pedroso reported ha ing met with one case since 1910 In 1922 Terr *et al* described a new Brazilian c which resulted in the important disco ery that their organism was not only dissimilar to that isolated by Medlar in the United States but lso that the parasit isolated by Pedroso and Gomez had been erroneously referred to *Phialophora verrucosa* Medlar 191 In fact t turned out to be form f *Acrotheca* Brumpt (19_2) identified this Brazilian species as *Hormodendrum pedrosoi* In 1924 Carini described tw new es of erruceous

dermatitis in São Paulo and made the point that in 1910 he had isolated from the big frog of Brazil (*Leptodactylus pentadactylus*) a fungus similar to the agent of this dermatosis

Montpellier and Catanei discovered in 1927 in Algiers the first case of African chromoblastomycosis and also incidentally the first case of this disease recorded outside the American continent They referred it to a new species *Hormodendron algeriensis*

Whilst fresh cases increasingly appeared in South America and elsewhere it was not until 1933 that Wilson Hulsey and Weidman reported the second North American case This second case from Texas was like the first caused by *Phialophora verrucosa* It was not until 1936 that Martin Baker and Conant reported having found a North American case caused by *Hormodendrum pedrosoi* In 1951 Vanbreuseghem Vandepitte Thys and Windey reported the first case of chromoblastomycosis in Central Africa and attributed it to *Phialophora pedrosoi*

This short historical account emphasizes the difficulties which beset workers in this field Other fundamental contributions whether of mycological or clinical interest will be dealt with more appositely in the text which follows

Importance and Geographical Distribution

In spite of the copious literature devoted to chromoblastomycosis the number of cases of the disease as yet recorded for the whole world has not appear to exceed 150–200 and it may be justly described as rare The chief countries where it is found are Brazil Porto Rico and Cuba According to Pardo Castello Rio Leon and Trespalacios who have made an extremely important contribution to the subject (194) chromoblastomycosis is relatively frequent in Cuba Beside these three main region of occurrence cases have been reported from the following countries South Africa Algeria Argentina Australia the Belgian Congo Costa Rica the United States Guatemala Japan Java Porto Rico Rhodesia Russia Dominica Sumatra Uruguay Venezuela Thus chromoblastomycosis though cosmopolitan is predominantly distributed in tropical and sub tropical regions

Etiology

Chromoblastomycosis is especially found in male adults w n being rarely attacked by it No race is immune and it is chiefly among the land workers that cases occur Wounding or wood splinters are usually involved before the disease is contracted and this is obviously related to the biology of *Phialophora*

The Agents of Chromoblastomycosis

The pathogenic fungi isolated from cases of chromoblastomycosis comprise three species within the unique genus *Phialophora* (Medlar 191) emend Emmons 1944 They are *Phialophora verrucosa* Medlar 191

Phialophora pedrosoi (Brumpt 1922) n comb Emmons 1944 and *Phialophora compactum* (Carrion 1935) n comb Emmons 1944. The genus *Phialophora* attributed by some to Medlar and by others to Thaxter was first described by Medlar in 1915. In this paper it was clearly stated that Medlar had consulted Thaxter but it is equally clear that Medlar claims the credit for the erection of the genus *Phialophora* and the species *verrucosa*. One of the figures from the work in question has the legend *Phialophora verrucosa* Medlar a fact which seems to be conclusive.

On the other hand Emmons who willingly concedes that genus *Phialophora* to Thaxter (in Henrici Molds Yeasts and Actinomycetes 1930) attributes the revision of the genus to three authors namely Binford Hess and Emmons (1944) though it is evident from the very title of the work that it is to Emmons that we owe this revision. The courtesy shown by the great American mycologist to his co-authors is understandable but not generally acceptable and the correct designation would appear to be *Phialophora* (Medlar 1915) emend Emmons 1944 and not *Phialophora* (Thaxter 1915) emend Binford *et al* 1944.

The *Phialophora* species are Dematiae with two forms of imperfect reproduction which may be found simultaneously or separately.

1. Unicellular phialospores scarcely or not pigmented may be produced in phialides—type *Phialophora*.

2. There may be acro nous pleurogenous or acropleurogenous production upon erect conidiophores of dark spores (type *Acrotheca*) or upon erect terminal or lateral conidiophores of spores in small chains (type Hormodendrum[1]).

This larger conception of the genus Phialophora is the result of the increase of knowledge of the mycology of blastomycosis. In view of the apparent conflict between Medlar's findings (1915) that the disease was caused by a species with a single form of reproduction and those of Terra *et al* (1922) who demonstrated the existence of another species with another form of reproduction it became evident eventually that several forms of reproduction could coexist in the same species. If the three known species are accepted as *verrucosa*, *pedrosoi* and *compactum* then apart from *verrucosa* which is unanimously attributed to the genus *Phialophora* the other species are variously distributed amongst the genera *Hormodendrum* (or *Cladosporium*), *Phialophora*, *Fonsecaea* etc. Thus in the literature *Hormodendrum pedrosoi* is as readily found as *Phialophora* or *Fonsecaea pedrosoi*.

It is important to recall that in 1937 Conant established on morphological bases that the genus *Cadophora* Lagerberg and Melin 1927 comprising various species discovered in wood pulp must give way to *Phialophora* Thaxter 1915 with which it shares characteristic reproduction by

[1] In our view *Hormodendrum* is correct and not *H*... Cf *Bo... d Hist fung Mycol* ... 1

phialides (*Cadophora americana* Nannf.) is thus synonymous with *Phialophora verrucosa* and the following *Cadophora* species pass into the genus *Phialophora*:—

Ph. fastigiata (Lagerb. and Melin) Conant
Ph. Brunnescens (Davidson) Conant
Ph. Lagerbergii (Melin and Nannf.) Conant
Ph. M l (Nannf.) Conant
Ph. repens (Davidson) Conant
Ph. Richardsiae (Nannf.) Conant

It is of interest that in 1938 Martin's study of complement fixation established the antigen similarity of a strain of *Cadophora americana* with several strains of *Ph. verrucosa* isolated from human, whereas other *Cadophora* strains isolated from wood pulp but differing in morphology from *Ph. verrucosa* belonged to a different antigen group.

The Cultures: Macroscopic

The morphology of the three species of fungi causing chromoblastomycosis varies according to the culture medium and the origin of the strains. In any case they differ but slightly from one another but it is generally agreed that colonies of *Ph. compactum* grow more slowly than those of the two other species.

In general the colonies vary in colour from very dark brown to olive black; they take the form of a flattened dome with a frequently mammillated summit, lessening in slope towards the periphery and terminating with a regular or festooned edge. Concentric or radiating furrows may be visible.

The colonies are covered with a more or less prominent tuft or dark brown down. For identification of the species microscopic examination is required, as the aspect of the cultures gives an insufficient indication. Examination is best carried out with hanging drops, which leave the spores in their proper place, whereas teasing out completely disturbs them. Cultures on agar slides are unsuitable for study, for the hard and very acuminate colonies cannot readily be compressed between slide and cover slip. Cultures on hair isolated in vitro (Vanbreuseghem 1950) are well suited for microscopical study of the morphology of the *Phialophora* species.

The Cultures: Microscopic

The vegetative mycelium of *Phialophora* does not vary from species to species. It is composed of rectilinear or undulated hyphae with thick and dark walls. The hyphae are segmented and branched, and their diameter is 1.1–3 µ. The chlamydospores recall the rounded cells found in tissues; they are rare, spherical, thick walled and 8–12 µ in diameter. Some chlamydospores are partitioned into 2, 3 or 4 cells.

The forms of reproduction of three pathogenic species are given

1 *Phialophora verrucosa* Medlar 1915 (Syn *Cadophora americana* Nannfeld 1937 *Phialophora macrospora* Moore and Almeida 1936)

The reproductive structures are contained in lateral or terminal phialides The conidia or phialospores are borne at the base of the funnel formed by the collar of the phialide The phialospores are not in small chains as in the next species but are aggregated in rounded masses held together by a viscous substance The phialides (3–4 μ wide by 4– μ long) occur singly or in groups The phialospores are ovoid and 1 –4 μ Besides this mode of reproduction there may rarely appear the same mode of reproduction as in *Ph pedrosoi*

Phialophora pedroso (Brumpt 19__) Emmons 1944
Synonyms—

Hormodendrum pedrosoi Brumpt 19_2	*Gomphinaria pedrosoi* Dodge 1935
Acrotheca pedrosoi da Fonseca and Leão 19 3	*Botrytoides monophora* Moore and Almeida 1936
Hormodendron algeriensis Montpellier and Catanei 1927	*Phialoconidiophora guggenheimia* Moore and Almeida 1936
Trichosporium pedrosianum Ota 1928	*Hormodendroides pedrosoi* Moore and Almeida 1936
Trichosporium pedrosoi Langeron 1929	*Fonsecaea pedrosoi* Carrion 194

This species generally reproduces by conidia borne on terminal or lateral conidiophores on the aerial mycelium (type *Hormodendrum*) or by terminal or lateral budding (?) of the vegetative hyphae (type *Acrotheca*) In the *Hormodendrum* type the conidia develop basipetally at the extremity of a conidiophore and remain in chains but each conidium may act as the starting point of a small chain of secondary conidia which in turn may yield tertiary conidia The conidia from which conidial chains originate are modified taking the form of an escutcheon (shield shaped spore of American writers) The unicellular conidia 3 μ long by 1 –3 μ wide are of dark olive colour and are connected to one another by thick interstitial structures In the *Acrotheca* type the conidiophores resemble a knotted stick yielding at each node an elongated and dark olored unicellular conidium

Apart from these two types of reproduction there may rarely be found in *Ph pedrosoi* typical phialospores as in *Ph verrucosa*

3 *Phialospora compacta* (Carrion 193) Emmons 1944
Synonyms—

Hormodendrum compactum Carrion 193	*Phialoconidiophora compactum* Moore and Almeida 1936

In this rare j w the sub phere l onidia (l r- μ by l μ) form compact masses of long bran hing hains arranged on lateral or terminal conidiophores



Fig 3

Ll hg l j l Ne th f l l j l

A ording t Curson (194) this species ha l en found in one se only n Port l co

Symptomatology

Chromoblastomy osis usually starts with a pustule or nodule onfined to lower xtr mity Frequently th patient call ttention to an anterior traumatism The foot and leg are especially ffected ne xt n order of frequency come the hands the forearm and the arm the neck the shoulders and the buttock The lesions with rare exception are unilateral

The pustule or nod le forming the primary lesion may become prurigmous This lesion enlar es congest run then becomes dry and erru ou It peripheral xtension is somewhat limited and t is mainly by multiple autoinoculations around the primary lesion that the latter enlarges and resembles after several years h g cauliflower formation The epidermis generally thinner at the surface of the lesion bleeds and ulcerate easily I other cases the pidermis is covered with scales and

scibe Young lesions are generally limited violaceous or dark red in colour and very infiltrated After frequent ulceration infection progresses regularly and the lymphatic become blocked At this stage the patient emits a repulsive odour

Metastasis is exceptional but not unknown The lymph nodes are usually left alone except in cases of secondary infection Merime (1938) claim however to have observed sclerotial cells in lymphatic gangl



Fig 4

Chromoblastom (C Vanbreuseghem Vanbr ... and W ...)

which also contained tubercular bacilli A strain of *Hormod. ... rossicum* was recovered from culture

Evidently the symptomatology of chromoblastomycosis is not yet well established which is to be expected in view of the relatively small number of known cases Generally speaking the lesion is regarded as a verrucous dermatosis and Carrion (194) made the interesting observation The more highly pigmented the lesion the less it will ... affected also the surrounding skin

There is however a tendency toward a fuller study of the symptomatology which may well bring about a modification of the definition of chromoblastomycosis increase the difficulties of differential diagnosis and ... result in the discovery of a greater number of cases

Carrion and Silva (1947) distinguished five types—

1 A nodular type at the beginning the nodule ... deeply coloured with a smooth verrucous or squamous surface

A tumoral type with papillomatous masses sometimes ... like cauliflower

3 A erruco u ty] m which the nodul or tumoral mass are hyperkerat cd

4 A blotchy type rare squ mou stains sh htly ele ted deeply oloured

A cicatricial type haracterized by a healing of the ntre f the lesions whil they sprea l at the circumf rence The centre is replaced by n trophied scar

A study of 31 case in C b by Pardo Castello I ro Leon and Trespal cios (194) ha resulted in the followin classification—

1 Verrucous type	1 ca
Tuberculoid ty]	4 cases
3 Syphiloid type	4 cases
4 Psoriasoform type	4 cases
Cicatricial and ele phantiasi type	4 ca e

The *Phial phora* species can cause other clinical lesions besides the las ical hromoblastomyco is From a generalized onyxis which the uls were opaque fri ble and brown Aroeira N ves (1930) isolated a fungus which he identified *Acrotheca pedrosoi* Again Emmons by transf rrin *Torula Jeanselmei* Langeron 19 8 t the genus *Phialophora* sh wed at the same time that *Phialophora* species may be ag nt of mycetomas

Histopathology

The hist patholo ical picture is that of an infectiou granuloma The pidermi is generally hypertrophied w th hyperkeratosis not bl acanthosi and elongation f the interpapillary processes Polynuclear leucocytes sometimes infiltrat into the epidermal layers and can ev n form small ab cesses there I the dermis occurs bundant infiltration f lymphocytes plasmocytes lar e mononuclears polynuclears eosino phil Russel bodies epithelioid cells giant lls of Langhan nd f foreign body type respect ely Thi infiltration whether localized or diff e is mainly dev loped in the superior dermal parts the papillae of which are hypertrophied Frequently miliary bsces es are encountered rarely necrosis The organism isol ted or in groups are free in the dermis or pidermis in the dermi they are often included in giant cell

Treatment

1 Surgical

M t workers adm t that either xtraction r lectrocoag l tion of the initial lesions (followed by per ce t gentian violet ppli ation accord ing to Pardo Castello 194) must be employed However en in littl ad an ed cases relapses re frequent

2 Chemotherapy

There is no agreement t the re l lue of potass um iodide ad ministered *pe os* f ry long time and in very stron dose (p to

10–15 µ per day) and of odium iodide intravenou ly (1 g at the tart reaching 9 g after some month) Martin Baker and Conant (1930) have in one case used iontophore is with copper sulphate with ome success

3 **Radiotherapy**

This has lon, been used Pardo Castello *et al* (194) obtained re ult in superficial form by admini tering 600–1 00 r filtered by 1 mm of aluminium

Besides these therapeutic measure designed to suppress the disease secondary therapeutics for the disinfection of ti sues attacked will take



Fig

H hoplor pel n S l tie ll of l tissu f m
(Case of Vanl ough m Var l pt 71 and Won)

a predominant place in ad ance l stag of the di ea E n t thi stage tincture of iodine added to 10–20 per cent alcoholic a id applied l ally brin, about some reduction of the le ions

The problem i really one of arly diagno is Sin unt l now only xtraction and electrocoagul tion have gi en definite re ult in the youn, form an early diagn i i obviously very important

Prognosis

Chromoblastomycosi i a di a e of ery long duration So far a is known up t recent years most li gno have been mad lesion f

30 y u standing a c s is known where the les se was pr nt for 40 years The di ease is therefore *quod t tam* benign one It becomes of importance only when th tissues re affected the lymphatics blocked and a certain degree of elephantiasis is de loped Sometimes in these es amputation of limb has t be considered though m g nerul it may well le th t local care hemotherapeutic measures directed against secondary infection and partial xtraction by lim ted and m ceous electrocoagulations may delay an operation or postpone it indefinitely

Differential Diagnosis

Though the symptomatolo y of n e t bli hed chromoblastomyco is may be sufficiently typical to require only simple laboratory confirmation this is far from true at the onset f the di ease There may be confusion with leprosy tuberculosis yaws syph li leishmaniasis monilia is and Gil hrist s disea At certain st ges a um the obscure mossy foot and *verrucosis lymphatica* (or *lymphatica verrucosa cutis*) might su gest a diagnosis of hromoblastomycosis

Mycological Diagnosis

Four method of pproa h may contribute to a diagnosis f hromo blast myco is —

1 *Clinical* As lready mentioned diagnosis is difficult xcept whe the di ease is fully established and it is lw ys unsaf t rely wholly upon l bor tory examination

Examination of the Pathoge ic F ngu Scales Epidermal Debr and T sue This may be carried out either by biopsy and an tom pathological xamination or by direct examination of crust o serum from the surfa mounted in potash

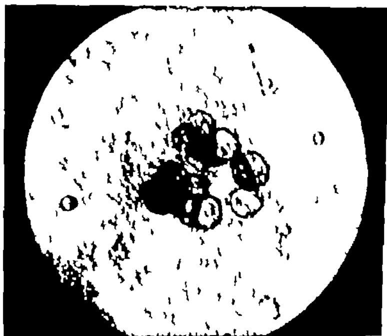
The organism concerned take the form of rounded bodies in the tissue occurring sin ly or in large numbers and surrounded by thick dark brown membrane They multiply by cell di ision nd not by budding The first division yields two cells which also tend to be rounded and these may di ide again w thout separation soon these lls which are not ob iously nucleated contain a granular oliv brown protoplasm and are about 10 μ in diameter In sections stained with Giemsa the ell wall ppears brownish green

Those who first described the disease ga the name sclerotic or sclero tial cells to the fungal ll found in the tissues This designation is ontroversial Langeron prefers to call them fumagoid cells Emmon ppears to ha adopted the term hlamydo pore which applied to ti sue forms is certainly an innovation It is interesting t note that de Area Leao Mello and Cury (1947) found in rats subjected to intratesticular injection nine months previously granules made up of dark rounded cells surrounded by cl bs lik gran les of actinomycosis Again Weidman

and I osenthal (1941) found lub like granule in a hum in se from whi h they i olated *Hormod ndrum pedrosoi*

In scales the fumagoid forms may be found to have given ri t filament

In section stron ly coloured fuma oid form are easily found either intra or extra cellularly in the dermis or in the superficial hyperkeratotic strata



F r

H lo ylor pedroso I rome ff f k l ue f n (C of Vanbreuseghem V l j tt 71 l Wm l)

I *In tomo pathological Examination* is c ncl si not ou t of the e idence to be gained of a specific histolog l pi ture which is th t of all infectious granuloma but becau e it j rmit the re v ry of fum goid forms *in situ* In ur xperien the form indi ate li no f chromoblastomycosis and the sp cies invol l an be t bli hed by ulture

Culture Isol tion in ult re i arried out at ordinary t mp ratur m Sabouraud test medium u in ither esk or mall fragment f tissu Binford Hess and Emmons (1944) f iled in one ase wh re th fragment f tissue u ed had probably be n sul jected to 9 per ce t tl yl lcohol and they recall a simil r failure by Wiedm n nd Ro nthal

Experimental Inoculation

1 It is first necessary to emphasize that animal inoculation does not result in a reproduction of the disease as it is encountered in man Human inoculation has however been attempted by Takahashi (1937) who successfully inoculated an individual already subject to chromoblastomycosis by making the inoculation in a healthy region and also an individual compensated for the disease

2 Even in Macacus rhesus the intradermal or subcutaneous inoculation of cultures end with the formation of nodules or abscesses in which is found the same fungal form as in the human disease

3 Intratesticular inoculation has mostly been studied in the rat An inflammatory orchitis first appears followed by abscesses within some months

4 Intraperitoneal injection in the rat or mouse provokes the formation of nodules on the mesentery and other intraperitoneal organs

5 By the intraperitoneal route de Area Leão, Mello and Cury (1947) using culture obtained from the clubbed granule developed in rat testicle obtained generalized lesions in the mouse These would appear to be exceptional

Conclusion

Chromoblastomycosis is a mycosis caused by accidental injection with several species of *Phialophora* Diagnosis is readily established by observation in the tissues of fumagoid forms also called sclerotic cells or chlamydospores Therapeutic measures have but little effect upon the disease which is of long duration

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Coccidioidomycosis

Definition

Coccidioidomycosis is an infectious disease caused by *Coccidioides immitis*, very benign and scarcely even noticeable at the time when it is first contracted (respiratory or primary form); it may exceptionally give way to a serious form (secondary or progressive) characterized by a varied symptomatology and a high death rate.

There is in fact very little controversy about the name given to the mycosis; the synonyms which are generally applied represent only certain phases of the disease or indeed particular aspects of certain phases. Some of these are: Coccidioidal granuloma, Valley Fever, Desert Rheumatism, San Joaquin Fever and less frequently Posadas-Wernicke's Disease. This last name is applied to the disease as a whole and not merely to one aspect of it.

Historical

In 1892 Posadas and Wernicke discovered in Argentina the first case of a disease which they considered to simulate a mycosis and which they attributed to a protozoan. They published their results separately in 1892. The second and third cases were found in 1896 in California by Rixford and Gilchrist, who named the causal agent *Coccidioides immitis* and also considered it to be a protozoan. Ophuls and Moffitt (1900) established by culture in the third American case the fungal nature of the organism. In 1918 Giltner discovered the first case of coccidioidal granuloma in a bovine at San Diego, California. In 1932 Stewart and Meyer first isolated *Coccidioides immitis* from the ground at a place where four cases of progressive coccidioidomycosis had been detected. Dickson in 1937 proposed the new term coccidioidomycosis to designate at the same time the primary form (Valley fever) and the secondary form (coccidioidal granuloma) of the disease. In 1942 Emmons isolated *C. immitis* from desert rodents and in the same year with Ashburn described *Haplosporangium parvum*. These discoveries clarified a few points of the etiology of coccidioidomycosis but at the same time added their quota of confusion.

Importance and Geographical Distribution

Although the first case of coccidioidal granuloma was described in Argentina, it is now quite certain that coccidioidomycosis is almost

completely limited to the desert regions of the south western United States namely California Arizona Texas and New Mexico. Only four cases have been reported from South America all of them from the Chaco region of Argentina. One case has been reported by Fernel from the Hawaiian Isles three from Italy and possibly in 191 Hartmann and Schoo saw one case in Holland.

In the United States quite a few cases have been described outside the principal endemic zones but more often than not it has been possible to relate the occurrence to a previous visit by the patient to one of these zones.

It would be difficult to estimate the number of cases of primary coccidioidomycosis on record as they are so very numerous. The secondary form is by contrast always rare. According to Forbus and Bestebreurtje (1946) 6 000 cases of primary coccidioidomycosis were diagnosed in soldiers during the last war.

Coccidioidomycosis is a disease of all ages without predominance of sex or race. However the serious form is usually found in men and mainly in coloured races e.g. Negroes Indians Mexicans and Philippinos. In the latter it may be particularly serious. According to Smith Beard Whiting and Rosenberger (1946) the progressive form occurs four times more frequently in men than in women further Mexicans are 31 times more likely to have it than whites negroes 14 times and Philippinos 180 times.

Children living in endemic areas apparently contract at an early age a benign form of the disease detectable by the cutaneous test which immunizes them against further attacks. Young adults who are not immunized and who enter the endemic region appear to be most susceptible.

Laboratory infections caused by the inhalation of cultures may arise anywhere. Smith and Harrell Jr (1948) reported six cases of laboratory infection five of them with sub clinical manifestations and one which proved fatal. Nabarro (1948) reported a case which occurred in England.

Etiology

Two points appear to be important in an exact conception of the etiology of coccidioidomycosis—

1 This highly infectious disease is not contagious and patients having one or other form of the disease do not transmit it. This essential fact is in no way invalidated by the fact that laboratory animals may possibly be infected from patients sputum. Rosenthal and Routien (1946 194) have in fact successfully inoculated the parasitic form of *Coccidioides immitis* by insufflating the trachea of Guinea pigs with pus sputum and scrapings from coccidioidomycotic granuloma. It is noteworthy that the inoculating material kept at I C for 110 days retained its infectious power. In spite of the conclusion of these workers who believe that coccidioidomycosis must be regarded as a contagious disease until the

contrary has been pro ed the ab nce of any known ase of interhuman contagion points conclusively to the non contagious nature of coccidioido mycosis

It is known that d t from the soil is an important factor of infection if not the only one This fact emerges from geographical consideration from periodic epidemiology and from experimentation

A Geographical Considerations

Coccidioidomyco is is a disease of the desert regions of the south western United States Smith Beard Whiting and Rosenberger (1946) have shown that in the northern part the annual rate of infection is onl 0 5 per cent whereas it is 20 to ? per cent in the south This clearly established the possibility of a causal relationship between the sandy nature of the soil and the development of the disease

B Epidemiological Considerations

These have arisen comparati ely recently and are based essentially on the mass experience which resulted from the installation during the 1940–45 war of airfield in the south west of the United States In 1940 Smith had already demonstrated that the di ease is purely periodic that it reaches its maximum during the dry seasons of summer and utumn when work goes on in the field and had concluded that trans mission of the disease takes place ia dust E entually Smith Beard Rosenberger and Whiting (1946) by means of cutaneous tests with coccidioidin demonstrated that the number of new cases could be red ced by diminishing the formation of dust by the dev lopment of meadows by the tarring of roads or by the dispersion of oil Smith *et al* belie that dust blown by the wind distributes the infectious spores and that infection occurs through the respiratory organs They consider that rain in winter is favourable t the egetation on which *Coccidioide immit* is developed fact yet not proved and that in summer it combat infection by diminishing the dust

C Experimentation

In 1932 Stewart and Meyer for the first time isolated *C immitis* from the soil in Delano t a place near which four cases of progres e cocci dioidomycosis had been reported In 194_ Da is Smith and Smith isolated the parasite from the soil at San Benito California In 194 Emmons isolated *Coccidioide immitis* five times from 1?0 samples of earth collected in the region of San Carlos Arizona According to Emmons (1947) the technique for isolating *C immitis* from the soil is as follows The soil is first emulsified in 30 per cent solution of sodium chloride shaken then the large particles which accumulate at the surface are removed It is allowed to decant for an hour when the supernatant liquid is collected and diluted to the sodium chloride concentration of physio logical serum This is then entrifuged and cultured or else the sediment

is used for inoculation In practice the guinea pig gives the best result for inoculation

Thus a number of investigations have demonstrated the existence of *C immitis* in the soil and explain the infectious power of dust However there still remain the questions of how the organism happens to be in the soil whether it stays there and whether it develops there Some very stimulating new data has resulted from important studies undertaken by Emmons and Ashburn (194) Emmons carried out his observations at the San Carlos Indian Reservation Arizona a region in which coccidioidomycosis was unknown but where Aronson Saylor and Parr (194?) had obtained a positive cutaneous reaction to coccidioidin from more than 90 per cent of the Indian school children This observation had appeared to be so curious to Aronson and his co workers that Aronson and Gallagher had followed up with a test upon New York children at the same time (194) using the same antigen and had obtained a completely negative result

In the same region of San Carlos Emmons caught 203 wild rodents and was able to record that 15 per cent of 1 4 mice (pocket mice i e *Perognathus baileyi P penicillatus P intermedius*) and 1 per cent of 29 rats (Kangaroo rat i e *Dipodomys merriami*) were infected by *Coccidioides immitis* This organism produces in these rodents a pulmonary mycosis characterized by nodules distributed in the peripheral rather than in the central parenchyma and these nodules may be calcified A curious fact is that 113 captured specimens of *Peromyscus eremicus* showed no sign of spontaneous infection by *C immitis* though this animal is very sensitive to the experimental inoculation of the disease

Besides *C immitis* Emmons isolated another fungus belonging to the genus *Haplosporangium* Thaxter which he called *Haplosporangium parvum* This new organism produces microscopic granulomas in rodents of the genera *Perognathus* (69 per cent of 1 4) *Dipodomys Citellus* and others

From *Haplosporangium parvum* Emmons was able to prepare haplosporidin which gave 29 positive reactions out of 33 individuals reacting positively to coccidioidin This interesting pathogen will again be referred to when dealing with haplomycosis

Certain hypotheses emerge from Emmons's observations and an obvious first question is whether though *Haplosporangium parvum* has not yet been isolated from man this organism is not responsible for a certain number of positive coccidioidin tests In fact it is easy to suppose that *H parvum* which causes minute lesions in rodents may be able to produce inconspicuous disease in man What is more in considering the prevalence of *C immitis* and *H parvum* in rodents it is tempting to speculate upon the existence of an animal reservoir However it is still obscure whether like man these animals are merely receptive subjects or whether they are indeed essential for the maintenance of the organism in the soil

It is noteworthy that *Perognathus* and *Dipodomys* are rodents which

are restricted in their distribution t the desert reg on of the south western United States where *Peromyscus* which is not in nature infected by *C immitis* spread in northern regions of America A *Peromyscus* under laboratory conditions is rapidly killed when infected whil t *Perognath* and *Dipodomys* are merely chronically affected it may be wondered whether the role of *Peromyscus* is not limited by it h per sen itivity to *Coccidioid mm t*

Thus sev ral important points remain to be cle red up especially (i) the exact role of th soil in maintaining the inf ction and (ii) the possible intervention in man of *Haplosporangium parv m* a an agent of false reactions t coccidioidin The possibility immediately sugge ts itself of using this pathogen a an immunizing agent against coccidioido mycosis

Pathogenic Agent

The mycolog al study of occidioidomycos is simplified by the fact that only one pathogenic agent for it known namely *Coccidioid mmit* R xford and G lchri t 1896

The genus *Coccidioid* at present represented by only one specie ha synonyms—

Posad a Canton 1898
Oid um Ophuls 190 non Link
Blastosporid m Hartmann 1912(?)
Mycoderma (pro parte) sensu Brumpt 1913 non Persoon
Blastomycoides Castellani 1926
Pseud coccidioides Fonseca 1928
Geotrichum (pro parte) sensu Ba gal 1931 non Link
Scopulariopsis (pro parte) sensu Ota 1928 non Bainier
Glenospor sensu Castellani and Iacono 1933 non Berkeley and Curtis

The specie synonyms are numerous but unimportant since the binomial *Coccidioid immit* is the onl one used in recent publication they are—

Coccidioide pyogene Rixford and Gilchrist 1896
Posad (sic) esteriformis Canton 1898
Oidi m protozoides Ophuls 190
Oidium pyogenes Ophuls 190
Oidium immite Verdun 1907
Blastosporid m schoo H rtmann 1912 (?)
Zymonema immitis Mello and Fernandes 1918
Mycoderma immite Brumpt 1913
Blastomycoides immitis Castellan 1928
Pseudococcidioides mazzai Mazza and Fonseca 1928
Scopulariopsis americana Ota 1928
Geotrichum dermatitid Bagal 1931
Coccidioid esteriformis Moore 193
Geotrichum immite Agostini 193
Geotrichum Louisianoideum Castellani 1933
Glenospora metaeuropea Castellan 1933
Coccidioides immitis ar typica Ciferri and Redaelli 1936
Coccidioides immit var pyogenes Ciferri and Redaelli 1936
Coccidioides immit ar metaeuropea Ciferri and Redaelli 1936

This parasitic fungus has the curious distinction of having been first described in Argentina where it is exceptional and of having been mistaken for a coccid by the first observers (Posadas 1892 Wernicke 189) Rixford and Gilchrist (1896) who named it considered it to be a member of the protista For this reason the validity of their denomination has been disputed though objections cannot really be supported Further some would attribute the first description to Stiles (*Coccidioides immit* Stiles 1896) who had been consulted by Rixford and Gilchrist this is incorrect for Stiles had merely given advice of a general nature It was not until 1900 that Ophuls and Moffitt demonstrated the fungal nature of the pathogen by cultural method

Parasitic Form of *Coccidioides immitis*

The organism appears in tissues or secretions as circular bodies named spherules or sporangia in which occur a very variable number of small spores called endospores or sporangiospores Rupture of the sporangial membrane liberates the endospores into the surrounding tissues where they are found free or phagocyted The endospores are 1 to 4 μ in diameter and are usually thought to have only one nucleus They develop into sporangia which at maturity are 20 to 60 μ in diameter and sometimes reach 80 μ Various factors determine the diameter attained by the sporangia such as the strain involved nature of the tissue parasitized and the host species In mice and guinea pigs they are particularly large The sporangia approaching maturity generally exhibit a large central vacuole so that in mice for example where this is particularly clear the protoplasm may be reduced to a thin multinucleate layer closely adpressed against the sporangial membrane This protoplasm is divided by radial and concentric cleavage planes into multinucleate fragments which eventually lead to the formation of uninucleate endospores If it should happen that fewer protoplasmic cleavages occur the sporangium may be found to contain rounded multinucleate masses instead of a large number of uninucleate endospores

The wall of the spherule may be 2 μ thick and usually has a smooth outer surface It has however been observed to be covered with excrescences and this has led Henrici to speak of actinomycetoid form

All workers are agreed that the spherules of *C immitis* do not bud However Delamater and Weed (1948) have claimed to have seen budding not only in their own isolated strain but also in those isolated by other workers This observation must be accepted with extreme caution

Emmons (194) showed that the endospore nucleus has the same morphology as characteristic fungal nuclei It is surrounded by a delicate nuclear membrane and possesses one eccentric nucleolus

Culture Morphology Macroscopic

Coccidioides immitis grows rapidly on Sabouraud medium After two days at 25 C slightly elevated circular colonies which are quickly

covered with a white down which browns on ageing may appear Often well developed in the centre this down is usually less prominent at the periphery The under surface of the colonies is dark near the centre There are somewhat large variations in the aspect of the colonies according to the strain some being able to form a lemon yellow pigment and others remaining membranous and smooth

Culture Morphology Microscopic

The vegetative mycelium is composed of segmented hyphae of diameter 1 to 4 μ Emmons (194) drew attention to specialized sporophores borne upon hyphae characteristic of young cultures which in his view were typical for *C immitis* Lateral branches appear upon the vegetative hyphae of the same width as those upon which they arise they rapidly double their width however and may produce secondary branches Each of these becomes subdivided into short segments 2 to 4 μ long in which the protoplasm condenses these are the arthrospores or chlamydospores of Emmons In older cultures chlamydospores appear to occur in various regions but it is probable that the typical sporophores are similarly formed

Protoplasmic condensation within the arthrospores may occur at the centre or against one of the septa if the protoplasm of two neighbouring arthrospores condenses against a common septum the usual symmetry is disturbed The arthrospores which readily break up in old cultures remain together grouped in pairs or small chains in young cultures

Baker and Mrak (1941) obtained from old cultures spherules analogous with the tissue forms containing endospores and of diameter not exceeding 10–20 μ Their occurrence must however be regarded as exceptional

Symptomatology

It was not until 1937 that Dickson established that San Joaquin fever and coccidioidal granuloma are of one and the same origin the former being merely a stage of the latter The same worker proposed the distinction between the primary form of coccidioidomycosis corresponding to San Joaquin fever and the secondary or progressive form which is coccidioidal granuloma

1 Primary Coccidioidomycosis

This form appears 10 to 14 days after exposure to dust in endemic regions It is characterized by pulmonary symptoms which are scarcely noticeable cough usually without expectoration pleural pain slight temperature (38 C) asthenia anorexia headache night sweating In the majority of cases normal health is restored in one or two weeks Sometimes a generalized and temporary maculous rash appears Radiological examination made at this stage reveals in 80 per cent of the cases pulmonary changes which may include—

1 Hilar infiltration

2 Infiltration of the pneumonic typ in the middle or low r region of the lungs

3 Single or multipl nodular le ions chiefly ituat d in the middle lower regions These nodules may di appear or become ex t like cavities with thin partitions which either soon vanish or may persist for sever years and become calcified In nine cases out of ten the cavitie are and in one eighth of the cases they are apical

4 More rarely mediastinal and hilar adenopathy occurs

5 In one fifth of the cases a pleural effu ion may be noted

The form of the cavity associated with pulmonary lesions ha give rise to a somewhat abundant literature According to Smith Beard an Tail o Saito (1948) these cavities which may be pre ent from the beginnin usually disappear after three or four months but are able to persi t for long as ten years They cannot be regarded as belonging to the progr form of the di ea e Mostly they are well tolerated (as for example in th se of a soldier rested on account of a lesion of this nature who indulge *violently in sport without any prejudice to his recovery)* Sometime however they are complicated by hemoptyses or hydropneumothora (2 6 per cent of the cases) The ame authors hav b erved cavitation in 2 to 8 per cent of hospital case which fact doe not e tablish the re frequency of pulmonary cavitation for the greater number of patient ar ambulatory On the other hand a mixed occidiodal and tub rcul infecti n was found in 7 out of 274 cases

From 2 to 20 days after the beginning of re piratory ymptom llergic manifestations appe ar in 2 to 5 per cent of the patient The ar either *erythema nodo um* localized particularly in the le but al in th arm buttocks thigh and scalp or *erythema mult form* localized in th hands face and neck Possibly there i coexistence of the two form Th name Valley F ver wa appli d to these form th ugh the whole o the primary f rm tend to be lumped together under this de cription The old appellation De rt Rheumatism arose from th app arance rare though it be of an inflammation of the articul tio f th knee instep Occasionally a phlyctenular conjunctivitis is found

In 100 ases of primary occ hioidomy o i Willett and We (1 have ol erved the following lini l manif tation fev r l ting le than a week 80 per nt thoracic p in 3 per nt ..... 61 per cent sputum blood streaked 31 p r nt articul r symptoms 8 per c nt *rythema nodos m* 4 per cent *ryth ma multiforme* p r nt malai 43 per ent anorexia 30 pe cent ..... 7 per nt .....

1 per cent

In 60 per cent of ca xpo ure to inf ction du t is not f llo ed by ymptom but unnoticed illne le elops and re eals it elf l y positi reaction to coccidioidin How er not all th exp ed t nf ction lev lop clinically dete table or unapparent illne Smith Beard Ro enberg r and Whiting (1946) ol rved that ..... at f 2 ndi iduals (r 4 p r cent) at first ..... to ..... oidin

become positive reactors. Thus we do not know the exact sensitivity of man to *Coccidioides immitis*. But what is certain is that only 1 per 1,000 of those who have had the mild primary form develop the secondary progressive form which is nearly always fatal.

Primary non-pulmonary forms of coccidioidomycosis have been described (Conant *et al.*, *Manual of Clinical Mycology*, 1947). These cases seem all the more doubtful because coccidioidomycosis can develop without symptoms and that moreover it is not yet proved that only those previously having an apparent primary form develop the progressive form.

2. Secondary or Progressive Coccidioidomycosis

This form, corresponding to the old coccidioidal granuloma, appears in 1 per 1,000 of those who have exhibited the primary phase. It is usually fatal. The progressive form appears during the weeks or perhaps months which follow the primary phase. It lasts from a few months to a year or more. Such symptoms are observed as light fever, anorexia, asthenia and rapid diminution in weight. The lungs exhibit a very pronounced pulmonary condensation and infiltrations reminiscent of tuberculosis. Bony lesions with the appearance of cysts are found particularly in the ribs and the small bones of the hands and feet. The lymph nodes, joints, skin, subcutaneous tissue, meninges and the brain may be involved. Meningitis complicates the progressive form in 30 per cent of cases.

In contrast with what occurs in South American blastomycosis, lesions of the gastro-intestinal tract are exceptional in coccidioidomycosis. Duemling (1949) has however recently reported two cases amongst coloured people infected at San Diego.

Histopathology

There is little information on this subject. As indicated by the name formerly given to the progressive phase of the disease, the essential lesion is a granuloma. The nodules resulting from the accumulation of these granulomas may abscess or calcify. In all cases the picture is that of a tuberculous lesion at the corresponding stage. The only distinction between coccidioidomycosis and tuberculosis is the presence in the former of the characteristic spherules found free or within giant cells.

Treatment

Symptomatic treatment is effective with the primary form. The presence of cavities within the lung demands care though usually they respond well. Treatment of the progressive form has up to the present been completely disappointing. No result has been obtained by the use of iodides, sulphonamides, penicillin, gentian violet or specific methods. Jacobson (1932) recommended the use of an extract from *C. immitis* consisting of a mixture of a filtrate from culture and one from macerated

organisms Injection of this has brought about an improvement and even cure in certain cases

Prognosis

Extremely favourable in the primary form it is very grave in the second ary form which almo t invariably terminates fatally within some month a year or sometimes longer

Differential Diagnosis

Diagnosis of coccidioidomyco i must be con idered in connexion with all patients living in the endemic zones or who have re ided there It is al necessary to remember that the handling of cultures is very dangerous and that all those who work in laboratories where strains of *C immitis* are kept are susceptible to infection The three cases in Napl reinforce the possibility of infection outside the endemic regions Primary coccidioido mycosis may obviously be confused with any of the benign respiratory diseases The progressive form is reminiscent of a number of di e es too large to enumerate It can be stated simply that it is capable of pre enting the symptomatology of the numerous di eases involving neoplasm or of microbial or fungal origin

Diagnosis

Coccidioidomycosis may be diagnosed in four different ways by micro scopic examination culture animal inoculation and by cutaneous tests and serology

1 Examination of the Pathogen in Exudates and Tissues

Pus or sputum often scarce in the primary form may be examined between slide and cover slip or in a drop of 10 per cent caustic potash The same may be carried out with pleural liquid or gastric content The characteristic cell already d scribed may be found with some difficulty

According to Jacobson (1948) diagnosi may easily be obtained by diluting pus or sputum with physiological serum between slide and cover slip then sealing with paraffin Germination of the pherule occurs *within a few hours and germ tube appear in* all directions Diagnosis in this manner requires one or two day

It is of interest that Willet and Weiss (194) could d mon trate the presence of the parasite by direct examin tion of sputum in only 8 out of 100 cases whereas by culture it could be isolated from 98 per ent of th cases

Section may be stained with sin haematoxylin or (m

2 Isolation in Culture

The cultural requirement of *Coccidioid mmit* r rs simpl Arta Le o and Cury (1950) showed recently that this fungu i auxo autotrophic r quire no itamin for it de lopment Thus it may

be easily cultured upon the usual media and also upon synthetic media lacking vitamins. It grows well at laboratory temperatures.

Cultures should be made in tubes rather than petri dishes as the latter entail too much risk of exposure of worker to contamination.

Certain media have been recommended as discouraging the development of contaminating organisms, for instance that evolved at Stanford University:—

Ammonium chloride	1 g
Sodium acetate	1 g
Potassium dihydrogen phosphate	0 8 g
Agar	g
Water	to make 100 ml

Autoclave 10 minutes at 1 lb pressure and before tubing out add 0 04 g of copper sulphate per 100 g of medium. This prevents the development of most bacteria. Smith recommends this medium.

St Wilhelm (1946) in view of the great tolerance of *C immitis* toward variation of pH (2 0 to 12 15) recommends the following:—

Bacto tryptose	0 g
Sodium chloride	5
Bact agar	20 g
Water	to make 1 000 ml

Place in 100 ml flask, autoclave and whilst the medium is still hot add 5 ml of normal hydrochloric acid, then place in petri dishes. Inoculate copiously (0 to 0 5 ml of sputum per petri dish) and incubate at 37 C. From the beginning of growth which occurs in 3 to days remove from the incubator to avoid desiccation.

Wilhelm also recommends the use of 1 : 2 000 methylene blue or acriflavine at the same dilution in the tryptose agar or together at the same concentration.

For microscopic examination submerge the petri dishes for 10 to 15 minutes in 10 per cent formol; this does not alter the essential morphology.

It is also worth noting that techniques employed with sputum (acid fixation digestion) for the isolation of Koch's bacillus destroy *C immitis*.

Usually the morphology of the colonies and their microscopic examination will establish the identification of the fungi. However in a certain number of cases animal inoculation must be resorted to.

3 Inoculation

This can be made from pathological or cultural products. Two animals are normally employed: mice which reveal the parasitic phase within 5 or 6 days in intraperitoneal injection and in any case die within 7 to 14 days, and guinea pigs which after intratesticular injection develop an orchitis and the aspirated pus obtained towards the fifth day is rich in spherules filled with endospores.

Inoculated chlamydospores whil t undergoing transformation t sporangia may remain attached to one another thus yielding clu ters of two or three sporangia which may present abnormal pictures of prolific development or of budding

4 Cutaneous Tests and Serology

Substances develop in the culture media of *Coccidioides immitis* which when injected into the skin of patients and those recovered from coccidio idomycosis produce a reaction analogous to that which tuberculin gives in those individual made sensitive to Koch s bacillus Tho e active substances which are probably poly accharides resist autoclaving at 15 lb for 30 minutes In 24 hours they partially dialyse through C llo phane membranes The substance in question coccidioidin can be kept indefinitely but is liable to destruction by bacterial contamination

For the preparation of coccidioidin C F Smith recommends culturing several strains of *C immitis* for two months in the following medium—

Ammonium chloride	g
I asparagine	g
Potassium dihydro en pho phate	1 31 g
Sodium citrate	0 90 g
Magnesium sulphate	1 5 g
Iron citrate	0 30 g
Glucose (quality cerolose)	10 g
Glycerine	ml
Water	to make 1 000 ml

E ch of these substances is dissolved separately in d tilled water and they are added in the above order to the asparagine Complete by dissolving the gluco e and glycerine and finally having brought up the volume to 1 litre sterilize at 115 C for minutes After culturing for two months the filtrate is diluted and 0 1 ml of a 1 1 000 dilution is used for testing After 48 hours erythema and induration are apparent Tho e who do not react are given another test in which the 1 1 000 is replaced by a 1 10 dilution

Stewart and Kimura (1940) defined the coccidioidin unit (skin unit) as follows A skin unit is the smallest quantity of coccidioidin which in a 0 1 cc do e produces in sensitive subject in 4 hours an rythema which lasts for 4 hours

The cutaneou reaction to coccidioidin ppears from t I day after the first ymptom to 10 days to 6 week aft r inf tion and persi t for years so that when positi e the only pos ible conclusion i th t the patient had or ha occidioid mycosis In serious cases of the progressive form the reaction may be negati e

I recipit n et ve with cocci ioidin may be demon trated in the serum of pati nt r those wh h e be n cured but u ually the precipitins

beapp ar within a month or tw f re rs (f Smith Bl nl and Iarko Sart 1948)

Complement fixation studies employing coccidioidin a antig n giv doubtful or poorly marked re ult with the benign forms but rise of titre indicates an aggravation of the condition

Study of blood sedimentation which incr during the period of invasion and that of dis mination may lso be of alue In three out of four of the cases of pulmonary involvement with cavitation there is on the contrary a normal sedimentation rat

Willet and Weiss have not d i the prim ry form a to 18 per ntag of eosinophils during the first week

Coccidioidomycosis in Animals

Animals are pparently not subject t the primary f rm of the disease The granulomatous form is the one encountered and more often than not d agno is is made at the post mortem

Except for rodent the greatest number of cs ha been described for bovines the first wa reported by Giltner (1918) at S n Diego California All the sick animals come from California Arizona and New Mexico Lesions in the bronchial ganglia or mediastin or more rarely pulmonary nodules re found on killing the animal Incision yield den e y llow pu remin scent of that of ctinomyco is

Microscopic lesion are tho of t berculo is but the pre nc of spherules establishes the diagnosis Spherules surrounded by eo inophilic clubs comp rable with a tinomycotic ro ettes hav been found especi lly n cattle

According t Smith (1948) a case of coccidioidomycosi ha been f und in a gorilla (*Gorilla beringeri*) and one in an American pe (*Cebus hypol u*) the zoo t San Diego California

In the dog coccidioidomycosis re embles the human pro re si form more clo ely than the ery chronic form in cattle In the three cas described nodules were found in the lung li er spleen kidney and brain Tw of these dogs li ed or had l ed in endemic zones The third case is more curious (Plummer 1941 Radmore 1941) n ol ing a mal setter from Canada which had been m ted with a female from Californ Aft ha ing shown disturbances of the entral nervous system the dog w s accidentally killed Autopsy reveal d pulmonary and cerebral lesions of a tuberculous haracter but in wh ch the h racteristic spherules were found

W th the xception of rodent (*see* *ale* Etiology) animals do not ppear to play any role in the spread or maintenance of occidioidomy osis

Taxonomy

It is generally agreed w th Emmons that *Coccidioid* *immit* a phy myete How er H rtm nn (191) and lat independently Langeron (1927) w re the first to suggest this The pro f of ccepted in the form

presented is due to Emmons who demonstrated a perfect analogy between the formation of sporangiospores within the sporangia of Phycomycetes and the formation of endospores within the spherules. While admitting that neither sporophore nor columella are found in the tissues and that in culture the mycelium is richly segmented, Emmons affirms that *C. immitis* is undoubtedly a phycomycete and is more likely to be classed among the zygomycetes than anywhere else. Emmons also invokes the pathological similarity between *C. immitis* and *Haplosporangium parvum*, the latter generally being placed in the phycomycetes.

The fact must not, however, be ignored that where is the deductions of Emmons were made from the form of the pathogen in the tissues and not in culture, the latter is usually the basis of classification, and that in any case parasitic forms are almost invariably convergent forms. It may be significant that the tissue forms of *C. immitis* and *H. parvum* are very similar, whereas their respective cultural morphologies are very different.

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CHAPTER VIII

Mycoses caused by Dermatophytes

Definition

The Dermatophytes form a group of pathogenic fungi which have a marked affinity for keratin attacking skin hair and nails. The word Dermatophyte which now has a precise meaning, was formerly used in a much wider sense it denoted any member of the plant kingdom living upon the skin as a saprophyte or a parasite and in this sense certain bacteria were considered to be Dermatophytes (cf Sabouraud in *Dermatologie Pratique* art Dermatophytes Doin Paris 1900). It is impossible to say who first gave to the word Dermatophyte its present restricted meaning. It is to be noted that it covers only the fungi referred to the Gymnoascales by Matruchot and Dassonville and grouped in the genera *Ctenomyces* Sabouraud *Trichophyton* Langeron and *Epidermophyton*.

The greatest confusion prevails in the dermatological nomenclature in denominating diseases caused by dermatophytes whether in France or elsewhere. We feel that in the French literature the word *Dermatophytie* used for long, but not precisely, ought to designate diseases caused by Dermatophytes. The word ringworm is applied by custom to d[illegible] a of the scalp and glabrous skin but it is difficult to apply it to [illegible] eczema marginatum and to mycoses of hand and feet caused by dermatophytes. The term Dermatomycosis has too broad a meaning, for it may designate all skin mycoses whatever the parasite. The term Dermatophytosis has mostly been used for dermatophytic diseases of hand and feet.

It is not here proposed to suppress terms established by usage [illegible] ringworm eczema marginatum herpes circinatus Athlete foot. The plea is merely for a precise term denoting all dermatophytic diseases, which could be used thus: Dermatophytic disease (*dermatophytie*) of the scalp or *Dermatophytia capitis*, of the glabrous skin or *Dermatophytia corporis*, of the nails or *Dermatophytia unguium*, of the feet or *Dermatophytia pedis*, of the inguinal region or *Dermatophytia [illegible]*. [illegible] Mycotic onyxis should be replaced by dermatophytic onyxis or dermatophytic onyxis of the nails especially as it is probable that all the mycotic onyxes are caused by dermatophytes.

[illegible] Translated [illegible] Medical Research Council [illegible] H M [illegible] Office [illegible]

Historical

The hi tory of rin_ orm goc back to the most remot time nd precedes that of the Derm tophytes There is an ccount in the *Pree s de Teignes* by Sabouraud

Dermatophytes have been know for more than a century but thei detailed study dates from the most rly work of Sabouraud F w recent fic work ha been a immune t criticism his and the ffort of his student nd ev n of his opponent have served only t xt nd it value

In 1837 whilst studying the cutule f favus Remak noted that it w made up of mould filament but d l not connect the mould with the di ease In 1839 Schönlein of Z rich sho d th connexion betw n the di ease and the plant kin_dom

However it wa Grub a Hun_arian Jew xiled in P ris who was the pioneer From 1840 t 184 he di covered ccessively the f us parasite that of thrush the first trypanosome in the frog then the parasit of microsporia later th w call the ectothri Trichophytons of the beard and finally the endothrix Trichophytons of *teigne tond t* (Sabouraud 1936) Though he d scribed ery badly the symptoms of the di ses of which he d co red the parasit in the matter of ring worm he ommitted only one not ble error Describing the pilar lesion he makes hi parasites grow upwards like hair when they all grow in the opposit direction t har down rds (S bouraud 1936) Gruby first work is pape in the Paris Academie des Scienc (1841) in whicl he describes fa us and show that it can be distinguished by m roscopic xamination In the same y ar he reported the inocul tion f the fa u fungus into man and animal and that he had at l st succeeded n making it grow ev n on wood (S bouraud 1910 p 1) In 184 he di covered the trichophytons whi h Sabou aud l ter called *Trichophytons microides* and introduced the term porrigophyt s (cryptog ms of fa us mentagrophytes (cryptogams of the mentag s) and phtophyte (crypt gams of thrush) N xt in 1843 he described and named *Microsporum adou n* which Sabouraud redisc ered in 189 Quoting Gruby it is to be noted that the spelling of *microsporum* is not microsporon it is often written I shall call these cryptogams microsporum be use of the smallness of their spores and in order t commemorat in th new field of patholo y the name of the famous academician who by his outstanding researche on Muscardine[1] ha contributed greatly in directing ttention t the parasit plant which destroy l ing animal ti sues I propose the name *Microsporum* *dou* for the plant organism which constitut

[1] Itali Ago t no Bass I o d in 183 th t mu rd of tl lkw rm used b fu g (*B* *be ia*) Th s t first known ex mpl of l se d by pla p rasit Bass ol serv t ons p re eded l ose of B rk ley J t l a I l y rs Audou Dav t f th N t l H t y Museum I of rare l and ampl fied Ba (l gs Cf Ainsw th (G C) A century of m l al and ete nary my ology Br ish *Tr* *B t My l Soc* (19 1) 34 1 1 16 Redaell (P) l V aor l (V) Ago t no B s pre ursor of ompa at m cop tl ol gy *My p thol g* (1950) 2, 1 -4

Porrigo decalvans In 1894 Sabouraud once more found Gruby's work which had been forgotten for half a century and noticed that what he had described in 189 as *Trichophyton microsporon* (sic thus probably the spelling mistake) had fifty years earlier been described by Gruby under the name *Microsporum audouini* He immediately rectified his mistake (1894) which was not merely one of bibliography but also one of observation because as Sabouraud himself wrote (1910 p 0) *Trichophyton microsporon* the *Microsporum audouini* of Gruby was first described as investing and filling up the hair with small spores a mistake that Gruby did not make and which was corrected after reading his account Gruby's series of mycological publications ended in 1844 with an investigation in which he described *Trichophyton endothrix* without naming it Malmsten in 1845 introduced the neologism *Trichophyton* in a paper translated into German in 1848

In 1845 Remak published the account of his attempts to grow and inoculate the favus fungus which he named *Achorion schönleinii* He stated that he had successfully inoculated himself with the fungus Remak wrote Sabouraud (1910 pp 66–7) obtained on an apple a beginning of vegetation of which he gave an unequivocal microscopic drawing It was not however until 1886 that a series of pure cultures was obtained

Within the space of four years Gruby had recognized the organism associated with favus and also *Microsporum* and endothrix and ectothrix *Trichophytons* The clinical description which accompanied this mycological work was unfortunately so imprecise that confusion reigned for nearly half a century Alopecia notably was attributed or not to *Microsporum audouini* and some claimed that there were versions of it with and others without *Microsporum* The *Trichophytons* were no better resolved and Sabouraud was the first to be able to answer two key questions the first put by Kral of Prague at the Tenth Congress of Medical Sciences at Berlin in 1890 on the plurality of the achorions the other by Mégnin in 189 on the plurality of the trichophyton

Sabouraud (1864–1938) (cf Langeron 1938 Grigorakis 1939) was stimulated to study ringworm by Besnier and under the influence of Roux and Duclaux he applied Pasteurian method In addition he gained experience in the culture of Dermatophytes from Duclaux who shortly after Grawitz was the first in France (1886) to obtain pure culture of trichophyton and favus he also gained from the work of Verujsky (18) who besides contributing interesting information on dermatophyte culture was the first to report the external spores which he distinguished from mycelial spores

In his first work (189) Sabouraud distinguished between the *tr jae tondante* associated with small spores and that associated with large spores Further this work established that the parasitic forms did not represent single species but groups of species He ended the discussions between unicists and pluralist

In 1894 Sabouraud published through Rueff in Paris *Les Trichophyties humaines* a book containing an atlas and in which he described many species of *Trichophyton* and distinguished clearly the parasitic organism *Microsporum audoui* which until then he had called *Trichophyton microsporon*. As recorder at the International Congress London in 1896 he demonstrated by means of cultures and microscopic preparations the plurality of the dermatophytes and established his findings.

Adamson in 1895 described the growth of dermatophytes at the level of the hair papilla giving rise to 'Adamson's fringe' named after him.

In 1896 Bodin published his work on *teigne tondante* in the horse. This exerted a considerable influence on Sabouraud and from it emerged a clearer if still imperfect understanding of the pleomorphism of the dermatophytes which had until then been considered to be an aspect of symbiosis. 'In 1892–94', wrote Sabouraud (*Les Teignes*, p. 84), 'I was ignorant of the facts of pleomorphism known however to professional mycologists and I had interpreted these facts as a symbiosis in the same culture of two different entities but only one parasite. And many had accepted this theory of commensalism. Bodin in 1895 first brought symbiosis into question in connexion with microsporum of the horse. Together we appreciated the real nature of the facts of pleomorphism.' Regarding symbiosis Bodin had indeed written (1896, p. 60): 'This polymorphism is an occurrence so widespread amongst lower fungi that the hypothesis of symbiosis in some cases observed in trichophytic cultures seems to me if not doubtful at least warranting further mycological investigation. Already however some workers such as Kral had deduced from this polymorphism that all the alleged trichophytic species described as entities were only reversible varieties of one type' (Bodin, 1896, p. 60).

Duclaux (Sabouraud, 1936) was responsible for advising Sabouraud to call pleomorphism 'the forms of mutation ... which definitely alter the characters of a species'.

His work had reached such a stage that Sabouraud owed it to himself to attempt to resolve therapeutic aspects of ringworm. After trying to find a hypothetical scurf toxin he found that thallium acetate used up to 1897 in the treatment of syphilis and cystitis was 'an automatic means of depilation' (Sabouraud, 1936), but he soon discontinued its use particularly when in 1904 he discovered epilation by X-ray, a method which with Noiré he was able to apply *en masse* thanks to the X-radiometer of Sabouraud-Noiré.

Whitfield in 1908 identified and referred to the dermatophytes what he called dermatophyte infections [*dermatophyties*] of hand and feet, 'a group recognized by Hebra in 1860', and four years later, being infected himself accidentally with ringworm, he discovered and used upon himself the ointment which bears his name. Ainsworth (1951) quotes him as saying: 'I then rubbed in an ointment of 5 per cent benzoic and 3 per cent salicylic acids in soft paraffin and coconut oil for three days and it

disappeared I venture therefore to recommend the use of this ointment in superficial tinea

In 1910 Sabouraud published through Masson (Paris) that remarkable work *Les Teignes* which is really the third volume of a series devoted to diseases of the scalp

In 100_ Plato and Neisser isolated trichophytin and demonstrated the reaction to this substance by patients suffering from trichophytia. This was confirmed by Truffi (1914) but developed particularly by Bruno Bloch and his students (1928). The discovery by Margarot and Devèze (1925) of the fluorescence under Wood's light of hair infected by *Microsporum* permitted of early diagnosis and easy supervision of the cure as well as the detection of contaminated objects. The classification of Ota and Langeron (1923) and that of Langeron and Milochevitch (1930) based on the cultural morphology of Dermatophytes and the use of natural media brought about the transfer of the bases of dermatophyte classification from parasitism to saprophytism. These principles were again used by Emmons in 1934 to support a classification which because of its simplicity is now probably the most widely employed. This survey would be incomplete without mention of the work of Grigorakis (19) upon the classification of dermatophytes if only on account of the heated discussions which it evoked (cf Sabouraud 1929–0)

Importance and Geographical Distribution

The dermatophyte infection [*dermatophyt*] are cosmopolitan diseases found in men women and children without any distinction of race or profession. This statement however requires some qualification

1 *Age* Ringworm affections of the scalp are usually diseases of childhood that cease spontaneously at puberty. This is not however invariable. If left untreated favus contracted during childhood persists for life. Scalp ringworm due to *Trichophyton violaceum* persist beyond puberty without difficulty without however having the longevity of favus. On the other hand rare cases have been reported of the occurrence of scalp ringworm in adults. Felsher and Fenn ... (1948) have recently reported the appearance of a scalp ringworm with *Microsporum audouini* on a woman of 46 having two children also infected with ringworm from the same dermatophyte. Reiff (1949) found a scalp ringworm caused by *M audouini* upon a woman during pregnancy. This applies only to microsporums and common trichophytons and not to suppurated ringworms—kerions—that may be contracted at any a

The reason for the spontaneous recovery from ringworm at puberty has long been a mystery but recent work by Rothman Smiljanic and Shapiro (194) has offered a plausible explanation. The ... k ... has shown that fat obtained by extracting adult hair with ether inhibit the growth of *Microsporum audouini* at minimum concentration of 0. ... per cent the fungistatic power of the fat extracted from juvenile hair is only

one fifth of this Thi fungistati ctivity is connected with the fatty acids while cholest rol neutral fat and the unsaponifiable part have no action From two batches of 1 kg of ad lt hair have been xtracted 20 3 mg and 3 5 mg of ctive product respect v ly The fatty acids which behav fungicides belong to the aliphatic series between C nd C

Sex A curious and hitherto unexplained fa t about scalp rin orm is its predominance in boy a compared with girls in the proportion of about three t one This long known f ct w rediscovered by Catanei in North Africa (1933) and by Vanbreuseghem (1950) in Central Africa In particul r Catanei bserved for Muslim 6 per cent of favus in girls and 20 per cent in boy In non Muslims however the same writer find per cent in boys and 4 1 per cent in girls—1 4 per cent *Trichophyton* species in boy and 3 7 per cent in girls—but these statistics are for a smaller number of cases In subsequent work Catanei (1938) found 64 boy suff ring from ringworm as compared w th 9 girls and noted on that occasion th t in the Aures as in other regions of Alg eri scalp rin worm ha been ob erv d w th greater fr quency in boy than in girls

In the Belgian Congo Vanbreuse hem not d that 89 cases f ringworm due to *Sabouraud te langeron* were distributed among 64 boys and 4 girls Again of 68 ca lue t *Trichophyton ferrug neum* var *album* 4 were in boys nd 23 in girls *Langeronia souda e* ff cted 17 boy and girl On the other hand 10 boy and 9 girls had rin worm aus d b *T iolaceum* and 26 boy and 27 girls by *T glabrum*

During the r cent rin worm epidemic in the United St te Schwartz Peck Botvinick Leibov tz and Frasier (1949) found that in 490 cas caused by *M audoui* the ratio of boy t girls wa 6 1 S artz Rockwood and Clekbel (1949) in the United States study ng 289 cases of scalp ringworm ver a period of 6 y ars (1941–46) noted that 6 per cent of the patient were boy and 38 p cent girl and that *Microsporum audoui* ttacked thre t mes more boy than girls where *M lanosum* ca i attacked both sexes equally

The predominance f ringworm in boy compared with girls requ re the support of important statisti but it ppears t be well established Some ttempts h e been mad to explain these facts it is said that boys g t the hairdresser more ften nd are more exposed t conta ion and again that the more abundant hair of girls protect the skin of the scalp against the mplantation of dermatophytes B t these explanations hardly go far enough Extra tion of the ha fat of the hair of boys and girls by the technique f Rothman *et al* (1945) would possibly be more revealing

The capacity of certain species of dermatophytes to ttack one sex in preference to the other is an insufficiently demonstrated possibility

Dermatophytes of the f et appear to occur as frequently n men as in women Schwartz (1947) noted this after xaminin 1 393 men and 730 women of whom 28 per cent certainly had a mycosis 34 per cent had

doubtful mycoses and 38 per cent were free from clinical sign. Athlete's foot, however, seems to acquire real importance with men more often than with women, and no doubt this is the reason why the trichophytin reaction is more often positive with men than with women.

3. *Race.* At first sight it seems that all races are equally receptive to all the dermatophytes. There are, however, certain facts which appear to indicate a predilection of certain races for certain dermatophytes or *vice versa.* Catanei's observations in North Africa are instructive: he has observed that the proportions of favus and of trichophytia were different in the various population of Oran. The white natives had 18.1 per cent of favus and 15.4 per cent of trichophytia; the black natives 2.9 per cent of favus and 15.4 per cent of trichophytia. He concluded (1933, p. 75) that "the proportion of white families contaminated by favus is thus higher than that of negroid families; these results agree with what we had observed in the study of the relationship between ringworm and race for all the subjects of the region."

It is not easy to explain these observed facts. It may indeed be a pre-disposition of certain races towards particular dermatophytes. Again it is possible that a dermatophyte may be incapable of establishing itself in a position already occupied by another, a hypothesis which may derive some support from the relative scarcity of mixed infections.

4. *Profession.* Ringworm of animal origin is more usually to be found amongst those who work in contact with animals, such as farmers, veterinary surgeons and soldiers who are particularly prone to large-spored *Trichophyton.* The greater frequency of favus in rural populations has been attributed by some to an animal origin of *Trichophyton schoenleini*, but this fact is far from proved.

Dermatophyte infections of the foot, e.g. Athlete's foot, are supposed to be more common among those who use swimming pools and shower baths. The occurrence of a greater proportion of Athlete's foot amongst those who indulge in violent exercise seems to be well established. Njell, Keeney and Broyles (1945) found it on 89.9 per cent of 871 young military recruits. Montgomery and Casper (1945) claim that from 1940 to 1943 the American Navy had to send to hospital 14,069 recruits contaminated with dermatophytes, most of them localised in the inguinal fold and the feet. Muskatblitt (1933), in a comparison of 100 persons selected at random from a dispensary and 11 students, found signs of pathological change between the toes of 80 per cent of these 11 subjects. This diagnosis was confirmed by culture or microscopic examination of 4.8 per cent of the students and 28 per cent of the others. Vain attempts have, however, been made to find dermatophytes in swimming pool and upon the cement and wood of shower baths. Williams (1933–34) made 1,400 unsuccessful cultures in a young men's college. Schwartz (1947) showed that in the laboratory it is possible to maintain *Trichophyton gypseum* on wood or cement, but be

un ible t isol ite pathogenic fungi from the floor or cement of shower ths fter sever il hundreds of workmen l id used them However anbreuseghem and Willaert (19 1) i lated *Epidermophyton floccosum* om the sputum and urine of a patient w th H bra eczema marginatum ey showed that the receptacles used w re infected mechanically by the tient without his knowledg It is therefore prob ible that workmen pread fragments of pathogenic fungi when ha ing shower The fact at they re not found does not prov that they hav not been carried ere

It would se m that more than one ct vity must be in olved i n vironment which naturally favours the spread f the di ease such t v ties being accompanied by a lack of local hygiene even though mporary a in the case of soldiers marchin or fighting

If dermatophyte infections (*dermatophytie*) re cosmopolitan the me cannot be said for ind vidual dermatophytes It is lear that whik rtain dermatophytes are cosmopolitan others ha a ery lim ted ographic il range that every country and region possesses its particular ectrum of dermatophytes and that this spectrum is relati ly stable l as *Trichophyton violace m T rubrum Epidermophyton floccosum* and *l nomyces nterdigital* ha a world wide di tribution whil t *Tricho hyton ferrug ne m T lf rewm Langeronia soudane* and *Trichophyton ncentric* m seem especially to ha a more l m ted geographical range is moreover clear that each region—this term is a ague one—ha it wn dermatophyt flora comprisin a particular range of species with rtain species predominant Many examples m y be given—

Sabouraud (1910) out f 500 strains of dermat phytes solated lentified 147 *Microsporums* f human origin (13 *M audoui*) and 14 of nimal origin (*M can*) making a total of 161 microsporia or approxi ately 32 per cent The endothrix *Trichophytons* numbered 10 (*T raterıforme* 11 *T acuminat m* 5 *T violaceum* 30) or 44 per cent here were 15 strains of neo endothri 30 microids 17 megaspores 3 favus (*Achorion schoenleın*) and 6 *Epidermophyton ngu nale (floccosum)*

Forty years later (19o0) Degos and Ri aber reporting the dermato hytes isolated at the Saint Louis Hospital Paris analysed 811 cases of cab as follow microsporic ringworm 7 per cent trichophytic rin orm 16 3 per cent small spored ringworm 3 per cent large spored ingworm 3 2 per cent favus 0 per cent Thus they compared with an nalysis of 1 127 cases obtained between 1930 and 1937 microsporic ingworm 51 per cent trichophytic ringworm 29 per cent small spored ingworm 1 8 per cent large spored rin worm 0 6 per cent favu 7 6 per cent They noted that the trichophytons (half of them caused y *T crateriforme* and the other half jointly by *T acum natum* and *T violaceum* which is not ery far from Sabour iud results) are diminishin hat the micro poria in contrast are increasing (32 pe cent in 1910 1 per cent from 1930 to 1937 57 5 per cent from 1948 to 19o0) and that here is a marked increase in ringworm due to *Microsporum can* (30 t

40 per cent actually 1 per cent in 1930 to 1937 and 9 per cent in the time of Sabouraud) It is to be noted that in Sabouraud statistics referred to above the animal *Micro porum* due to *M. cani* (= *M lanosum*) appears in only about 3 per cent of the cases It is also apparent that there are 8 cases of microsporia caused by *M ferrugineum* upon children from the Far East and that there is an epidemic involving the same species in Jews from Central Europe living at the Central Accueil at Sèvres some of them having previously stayed in Tashkent Russian Turkestan

The apparently unique statistic of these French workers emphasize the persistence of the same species in the same places the variations in percentage of certain species possible over a large number of years and the accidental introduction of certain exotic species

During their studies of the ringworm of Eastern Scotland from 1946 to 1947 Kinnear and Rogers (1948) noted that most of them were *Microsporums* as against 613 cases caused by *M audouini* they found 8 due to *M canis* 5 to *T crateriforme* 1 to *T sulfureum* 1 to an unidentified endothrix *Trichophyton* 1 to an unidentified ectothrix *Trichophyton* and 2 favus In this result their almost 100 per cent microsporias contrast markedly with the 57 5 per cent of Saint Louis Hospital in 1930 and still more with the 3 per cent of Sabouraud in 1910

Coudert and Doucet (1950) in a brief account of the ringworm of the Lyon region from 1946 to 1949 pointed out that of 34 cases ... *Microsporum* (about 1 per cent) chiefly *M audoui* ... 66 ... suppurated ringworms (69 per cent *Ct mentagrophyte* 10 per cent *T album* 1 per cent *T rosaceum*) ... were favus (about 5 per cent) and 5 endothrix Trichophytons all caused by *T violaceum* Thus even though the picture may have differed appreciably from the Parisian one the species involved were the same and no exotic species were encountered

Cate Coudert and Chmel (1947) have on the other hand noted the frequency with which Ct mentagrophyt (3 cases out of) was found in the south east of France among st dermatoms ... of animal origin The proportion is certainly not met with in Lyon where Microsporums and ... ctinosporic are active in the etiology of ringworm of animal origin

Popoff and Zochareff (1940) estimate that T violace m is responsible for 60 per cent of ringworm in Bulgaria and in 1900 Nicolau asserted that in 1 ervations extending for four years he failed to find ... *Micro porum* and that most of the ringworm infections in Rumania are due to *T violaceum*

In Finland ... (194) after studying ... dermat phyt infection (*dermatophytie*) in man for four years found neither f... nor microsporia The endothrix *Trichophyton* (14 strains) were repre... ted only by *T violaceum* Other species isolated most frequently ... *Trichophyton gypse m gran losum* (... trains) *Epidermophyton ingui nal (flocc s m)* (... train) and *F ... g ... l* (19 strain) An investigat on of ... and Hare (1950) verified the absence f m rosporia nd f ... an ... l

T. schoenl i m Finland however *Achorion (Microsporum) gypseum* and *A. gall nae* which w consider to be *Sabouraud ies* were discovered.

Walker (1950) gave interesting information on dermatophytes isolated in Great Britain and Northern Ireland from June 1946 t September 1949. Out f a tot l f 473 strain the following were identified: 1433 *Microsporum udou* 544 *M. ca* 8 *M. gypse m* (t 1985 strains f *Micro porum* or bout 80 per cent) 39 *Trich phyton ulf reum* 42 *T. schoenlein* *T. violace m* 31 *T. d rosd* 53 *T. me tagrophyte* 1 1 *T. interdigit l* 97 *T. rubrum* 16 unident fied *Trichophytons* 7 *qu nckea m* *T. equ um* 4 *T. persicolor* 1 *Epidermophyton floccos m*.

Blank (19 1) gav some data upon tl rmatophytes of Sw tzerland but in it comment must be taken int consideration that two thirds of his train came from dermatophyt inf etion of the f et He solated *Sabouraudite udoui* 0 *S. ca* *S. gypse* 6 *Trichophyton schoen le n* 1 *T. flavum* 56 *T. rubrum* 78 *C t nterdigital* 9 *C t gran losu* 3 *C t asteroide* 9 *Epi lermophyton floccos m*.

Lehman l pkin and Reveman (1950) isolated out of 170 cases of scalp ringworm bserved in T xa from F bruary 1946 to August 1948 11 *Microsporum* (68 pe cent) and 5 *Trichophytons* (3 per cent) a follow *Microsporum lanosum* (ca) 90 (3 per cent) *M. udou* 19 (11 per cent) *M. ful m (gypseum)* 6 (4 per cent) *T. mentagrophyte* 23 (14 per cent) *T. to surans* 4 (per cent) *T. iolace m* 9 (5 per cent)

Lewis Hopper and Pe (1946) pointed out that during the ringworm pidemic of 1943 t 1944 in the United States 9 cases out of ery 10 were caused by *Microsporum* *lou* wherea before the epidemic *M. udou* nd *M. lanosum (ca)* were found w th equal frequency

Burke and B mgarner (1949) observed in the Un ted St te the following fungi t be the cause of mycoses of the glabrous skin on veteran of the second World War—

T nea ped 900 cases Positiv cultures 186 (1 per cent) F ngi isolated 118 *T. gypse m* (63 per ent) 8 *T. rubrum* (31 per ent) 4 *Epidermophyton flocco m* (per cent) 6 *Candida albica* (3 pe cent)

Tinea ngu um *T. gyp eum* w identified in 60 per ent of the cases

T. ca cru from 29 posit ultures 8 *T. gypseum* 10 *T. rubrum* 1 *F. floccosum* 4 *C. al ica*

T nea man out f 31 positi cultures 1 *T.* *brum* (65 7 per cent)

Out f 10 generalized dermat phyt infections (*dermatophytie*) *T. rubrum* w isolated 8 times from whites nd *T. gypseum* once on whit and once on a black

In Algeria Catanei (1933) laimed to ha e observed 320 ca es f favus caused by *Achorion schoenlein* and 528 cases of trichophytia From 94 per cent of 670 cultures of trichophytic hair he isolated *Trichophyton glabrum* and *T. violaceum* Se en other Trichophytons were also isol ted as follows (in order of frequency) *T. crateriforme* *T. fumatum* *T. ondanense* *T. regulare* *T. cerebriforme* and *T. sulfureum* Further he described tw new species namely *T. gourv l* (Catanei 1933) nd

T. pruinosum (Catanei 1931). Catanei had also isolated 1 *Microsporum audouini*, 1 *M. tardum* and 2 *Ctenomyces mentagrophytes*.

A further investigation by Catanei (1939) upon ringworm in the French colonies is best summarized by quoting the author. "A first investigation of scalp ringworm in the French colonies shows that the parasitic flora of these mycoses varies greatly with the country. The trichophytias observed in western and equatorial Africa are caused mainly by *Trichophyton soudanense*. *T. violaceum* is less frequent. Some cases are caused by *a new species of Trichophyton*, *T. gourvili*. The microsporia are caused by *Microsporum obesum* which appears to prevail, and by *M. audouini*. In the French Indies the trichophytias are caused by *T. violaceum* and *T. sulfureum*, the first species being the more frequent."

From 427 strains of dermatophyte isolated in the Belgian Congo Vanbreuseghem (1950) identified: 175 *Trichophyton ferrugineum* (41 per cent), 107 *Sabouraudites langeroni* (25 per cent), 80 *T. glabrum* (19 per cent), 27 *T. violaceum* (6 per cent), 4 *Langeronia soudanensis* (5.5 per cent), 13 *T. rubrum* (3 per cent), *Epidermophyton floccosum* (0.5 per cent). The hair lesions showed 68 per cent of microsporia and 32 per cent of trichophytia.

On the other hand Sagher (1947) published an interesting table which is reproduced below with some slight modifications.

Dermatophytes	A	B	C	D	E	F	G	H	I
T. schoenleini	9	160	9	0	9	1	3		)
T. glabrum	0	0	0	0	0	0	0	0	
T. acuminatum	1	4	0	(	9	0	0	0	5
T. crateriforme	3	100	1	0	(	0	0	1	4
T. cerebriforme			0	0	(	0	0	0	4
T. gypseum	78	(	1	0	0			113	19
T. violaceum	1		0		0	0	0	0	1
T. persicolor		0	0		0	0	0	0	1
T. faviforme	4	0	0	0	0	0	0	0	1
T. ...cu	)	1	0	0	16	0	0	0	1
M. audouini			11	00	0	0	0	114	(
M. felineum	(	0	0	94	0	0	(	0	0
M. lanosum	0	0	0	4		0	(	115	0
A. ...	91	(		13	0	0		1	4
E. ...	44		(	(	(		)	3	5
E. ...	0	0	0	0	0	84	1	8	24
T. ...	0	0	0	0	1		0	34	31

Note: A ... B ... C ... France; D Duncan, England; E Bogrov, Russia; F ... G ... H Lewis, New York; I Sagher, Jerusalem.

Sagher's patients came from Syria, Lebanon, Persia, Irak, Afghanistan, Yemen, Morocco, Central Russia and from several European countries.

The above information though incomplete nevertheless permits some conclusions to be drawn—

I. Every region studied has a dermatophyte flora characterized by the predominance of certain species.

This flora tends to ... from time to time. The variations in the dermatophyte spectrum are not however produced by the appearance of

species hitherto unknown in the region in question They are caused either by real epidemics such as the recent one in the United States produced by *Microsporum adoun* or result from the operation of unknown factors as is apparent in the ringworm studies carried out in the Saint Louis Hospital during the last half century where the microsporia have acquired a prominence that they lacked in S bouraud t me

7 It is a complete mystery why certain dermatophyte establish them selves in certain regions and not in others I tala and Harö (19 0) commenting upon the absence of *Microsporum* from Finland suggested that this m ht be related t climat They remarked that on two occasions they lost their cultures of *Microsporum* strain The Finnish workers probably er rat this f ct M ny mycological centre keep strains f dermatophytes from various countries often ry far w y w thout any more difficulty in keeping them liv than is the ca w th their local strains

The ob ervations of D. on nd Rivalier (19 1) on the xist nce of a source of *Microsporum* (or *T*) *ferrugineum* in France supply a interesting contrast of viewpoint Are xotic d rm tophytes likely to spread from this source? We do not thi k so but it is t be hoped that these Fr ch workers will continu t follow up thei int re tin observations

Etiology

Human scalp ringworm dise se are usually transmitted i schools hence the name *teigne scol res* During the recent epidemic caused by *Sabouraudite adoun* American work rs demonstrated the possibil ty of transmission via theatre seats and hairdressers instrument

Microsporums of animal origin differ clearly from the previous one in that an inf cted cat or dog is found t be their source D id on and Gregory (1933) demonstrated the difficulty of diagno is in the cat which can act a carrier without any rceble illness and the alue of Wood light in the detection of inf tion in nimals Sabouraud observed o cases of circinated herpes caused by family of Siamese t and produced by *Microsporum fel neum* (can)

The lesions and sycosi caused by small nd large spored dermatophytes are mostly due t direct contact with an infected animal Da idson Gregory and Birt (1934) bserved 46 cases of suppurated ring worm caused by *T all m* nd *T gypseum* All the patient were farmers or cattle merchant

Human fa u caused by *Trichophyton (Achorion) schoenle* occurs mainly in poor families especially in rural area In France there are constant sources of favus (Jura Somme Calvados) Favu of animal origin arises from contact with infected animals e g mice poultry

Current wo k by Vanbreuseghem and Van Brussel ha ing d m nst te l the d rmatophytes can be cult l on st l ed so l start ng th w th culture th infected h mals to y l l patho g stra may w ll be tha certain class l statements as to th et ology of the D rm tophytes w ll requ re con derable modif ca on in th ery near future

Hebra's herpes marginata and the dermatophytoses of the feet are probably favoured by warmth, physical exercise and lack of hygiene even though temporary. The part played by shower baths and swimming pools in their transmission is very doubtful. Spring and summer and a generally hot climate favour their development. Passing from a hot climate to a cold one often results in the spontaneous retrogression of harp clinical signs in the absence of treatment.

Keratolytic Power of Dermatophytes. Parasitism of Hair

It has long been known that the dermatophytes are able to attack keratin. This fact is easily verified by noting in a *Microsporum* or *Trichophyton* preparation on a slide the hair broken a few millimetres from or close to the scalp, or again by the examination of a nail attacked by *Trichophyton*

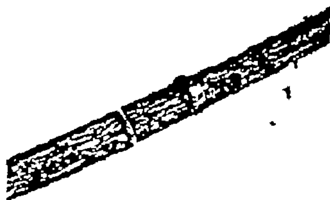


Fig.

Destruction of hair ... ... perforating organs

rubrum. The keratolytic power of dermatophytes may be ... *in vitro* as well as *in vivo*. This was first demonstrated by Roberts in 1894 and later by T... (1930) and Tate (1933).

Despite precise observation in earlier studies, it was generally thought that dermatophytes growing on hair *in vitro* pursue a morphological development identical to that which characterises them in culture media. This matter has recently (1953) been taken up by Vanbreuseghem, who cultured a wide and varied range of dermatophytes on hair *in vitro*. He demonstrated that:

1. The morphology of the fungi grown on hair *in vitro* is different from that characteristic of the parasitic state.

Different methods may be involved in the fungal invasion of the hair *in vitro*, namely, either by the penetration of perforating organs or

by the progress di slut on of th hair from the cort x toward the centre

3 The breakdown of kerat n can l ol erv l not only upon human but al upon the most ared animal h well on f athers

4 The dermatophyte re the only fung ble t tt ck hair in this w y

This pro ides a means of facil tating the diagno is of dermatophyte

Vanbreuseghem thus e t blished that there is a contrast between the de lopment f d rmatophyt the parasit and prophyt states respect ly

Tho who first studied the rin w rm f n from Gruby onwards directed their effort tow rds underst nding the li position of the para tic organi ms within and around the hair The lear descriptions f Sabouraud t the d po l f modern workers h v simplified many ones which must hav been complicated for the earlier work rs A an tance f a controver al que tion S bouraud him lf w long, unaware f the spore sheath of *Microsporum* Grul y who had previously noted it had given specifi reco nition to *Microsporum a lon* wheres S bouraud long regarded the organi m in question *Trichophyton microsporo* not knowing it listinctive morpholog l f ature

Most of the current knowledge f the mechanism of the n a ion of the hair at is due t the work of S bouraud nd to cert in E gl sh work f which that of Adam on (189) is the mo t important There is no bett r description of the mechanism f the penetration of the derm tophyte into the hair than th t f S bouraud g n in a summariz l form in 1938 (p 100) Imagine one f these propagules east upon healthy skin and about t de lop there The mother cell will surround it elf with many bran hes div rg ng lik the spokes f a wheel the result nt epiderm l lesion will thus l orbicular nd the rim of the wheel ill l the region of rapid mult pl cation f th para it These filament penetrating the corneal layer encounter the follicul r orific unt which the corneal epid rmi i inflected follow ng this th y descend into the follicle How er below the infund bul m the corneal pidermis is missing, so the parasite d prived of it only medium for growth ca n nd no further B t it is close t the ha which occupie the foll k and the hair is keratinized lmost t it base t the neck of the pilar bulb The parasit then lift the cuticle of the hair (the ells of which are imbricated one upon another like tiles but n the ppo t di ection t that of the growth of the hai so that the nearest cell covers th f rther one and thus presents a possible w y of penetration t the descending dermatophyte) and penetrates it H ing in aded it in depth with its filaments it goes down to the le el where the hair is no longer keratinized beyond which it is no longer ble to de cend (These terminal branches of the parasite mak up what ha been called Adamson fringe which is the real zone of growth of the dermatophyte) The bulb f the hair which is never in aded does not react to the para t nd continues it function

and so does the pilar papilla the hair therefore continues to grow as if it were not infected and so far as the hair is keratinized up to the level of the neck of the pilar bulb the parasite continues to invade it

With this noteworthy account in mind the various types of parasitic hair invasion will be described

A Favus At the same time as it invades the hair the organism usually accumulates around itself an aggregation of mycelium included in



Fig. 8

Destruction of hair by dermatophyte [illegible] showing [illegible] of the hair from the periphery toward the centre

the epidermis that it compresses beneath and around itself this is the favic scutula The hair is invaded by mycelial filaments which are divided into fairly long segments Here and there secondary filaments emerging from primary filaments divide several times in [illegible] giving rise to the configuration known as the favic tarsus or chandelier These are polygonal aggregations comprising 8 to 1[illegible] very short mycelial fragments disposed in a manner which vaguely resembles that of the tarsus [illegible]

B Microsporum The hair is surrounded by a sheath of small spores disposed without definite order in a mosaic Within the hair [illegible] found mycelial filaments which are usually barely visible [illegible] and descending toward the bulb The spores result from the fragmentation of the mycelial filaments into very small elements The formation of the sheath of peripilary spores is certainly at first independent of the development of intrapilary mycelium It is due to the subdivision of the mycelial

filament going down into the pilary infundibulum between the hair and the epidermal cells But Sabouraud admit (1910 p 199) that this sheath can be renewed and continued by the terminal ramifications of the intrapilary mycelium being able t graze the surface of the cuticle and end or there with slet of spores more or less close to one another

C Trichophyton The mycel l filame ts invade the hair completely and reduce i to very small elements of square or oblong section becoming progress ely rounded and forming regular chain The spore are larger than those found in the sheath f the Microsporum It w whilst studying the Trichophytons which produce this microsporic picture that Sabouraud coined the term endothrix of which the meaning ha subsequently not al ays been fully appreci ted moreover it ha been used both as noun nd an adjecti e In the first case t denotes dermatophytes which produce a pilar lesion similar to that just described Sabouraud (*Les Teigne* 1910 p 263) is worth quoting As early a 1893 I noticed (later than Gruby but without having read his text) that in the common *teigne ton le le* the Trichophytons had *ll thei pore chain ed n ely with a the ha* and for that reason I gav them the name Trichophytons *endothrix* Thus the word endothrix should only be used t denote that particular condition of the hair when it is filled with spores

D Microi les The dermatophyt no c lled *Ctenomyce* but which Sabouraud called microidal Trichophytons in ad the hair by means of filaments which are usually barely visibl also as in the case of the Microsporums they env lop the hair w th a sheath f small spores in little chains Sabouraud (*Le Teign* 1910 p 273) recognised a pur stic sheath compri ing three elements—

—Very fine (3 to 4 μ) shelled spores

β—Rows of spores like strings of be ids

γ—Delicate (μ) non segmented mycelia float ng in the preparation in the form of fragments 15–20 μ long

The type of le ion thus constituted was called *ectothrix* by Sabouraud though this term is more usually appl ed to the form described below

F Ectoth ix In this parasitic type filament which may be reduced to large spore are found in the hair further they are surrounded by filament reduced into small chain of ery large spores Confusion is possible neither with the microides nor with the microsporums and obviously not with the picture of fa u or endothrix trichophyton Again quoting Sabouraud (*Le T ignes* 1910 p 263) I noticed whilst ex amining trichophytoses of the beard that the hair was *not only invaded but also surrounded by mycelial filament* and I named trichophytons of this type trichophytons *ectothrix* This further quotation al o xplains much subsequent misunderstanding (note loc cit p 203) The definition

of ectothrix trichophytons has led to much confusion which I noted from the first especially at the London Congress. Most of the English workers believed that I considered the ectothrix to surround the hair without invading it and so Fox and Blaxal were able to write. Later researches appear to demonstrate that hair itself may be more profoundly implicated than Sabouraud at first observed and hence the term endo-ectothrix (An inquiry etc p) And this is how the term endo ectothrix whose definition is exactly the one I had given to the term ectothrix was created

F Neo endothrix Sabouraud had thus named type of pilar lesions characterized by the occurrence of spores in regular chains within the hair and with some filaments in an external position. The *neo endothrix* trichophytons he wrote (*Les Teignes* 1910 p 270) are certainly true endothrix for if a search is made amongst diseased hair *one can invariably find some presenting the typical aspect of the real endothrix* But amongst these hairs a certain number one out of four are found which exhibit around the hair some striped filament between the hair and the follicle or attached to the surface of the hair. This is symptomatic of the commencement of a trichophyton only when the real endothrix trichophyton is involved this invading period is so short that its detection necessitates careful observation whereas when it concerns the trichophyton of which I speak it is prolonged to the point that it is difficult not to observe it

Again Sabouraud wrote on p 263 Thus the various trichophytons may occur as four micro porn types in human hair

I True endothrix
II Young endothrix (neo [illegible]) [illegible]
III The ectothrix microsporum
IV The microid

However in *Nouv II Pratiq Dermatologique* (1930) Sabouraud abandoned neo ectothrix and dealt only with ectothrix among which he distinguished beside the microide certain parasites that appear to be of animal origin and that not only invade the hair after the manner of the endothrix type but also form around the hair a sheath of large separated filaments this is the ectothrix group and among the ectothrix type of animal origin there is a last group of species meriting separation because of the enormous size of their spore structures and which has been called megaspore (p 108)

The following conclusions seem to be drawn [illegible] type can be recognized in hair invaded by dermatophytes as follows

I The intrapilar filament type represented by hair parasitized by the agent of human favus namely *Trichophyton schoenleini*

II The microsporon type characterized by not ry clear intrapila filament nd by a sheath of small spores in mosaic g, *Sabouraud* *te* (*Microsporum*) *audoui*

III The true trichophyton or ndothrix type the hair is filled with spores in regular rows or chains At the mature stage f the in sion there



Fig)

Endoth l on ward l T *d ogl fro fl l* (HV 1 (8)
Th h *me inte l in cl lor il l topl emol era hed l gt l t l* ow
the intrap lar spores (400)

are no mycelial or spore bearing stru ture outside the hair Th type of lesion is produced by *Trichophyton ton rans*

IV In the ecto endothrix type filaments are found within the hai and according to th particular dermatophyt responsible for the lesion a sheath of small or large spores is found outside the hai In certain cases intrapilar spores may also be found This fourth group ppears to be confused and deserves complementary study in part cular such study should determine whether for a gi en species th parasitic type is constant or ariable In the case of th megaspores varying descriptions ha undoubtedly been gi en by writers whose capacities for accurat observ tion are unquestioned

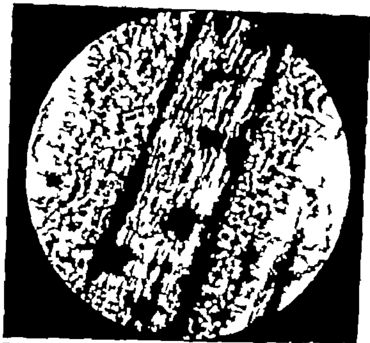


Fig 10 Hair of guinea pig parasitized by *Trichophyton* ... (strain I V 23 ...) Ectothrix lesion near ... pilar follicle Mounted in chloral lactophenol



Fig 11 Hair of guinea pig ... *Trichophyton* ... (strain ...) ... follicle ...

Classification of the Dermatophytes

Various classifications of the dermatophytes have been proposed. Three are given below: (i) that of Sabouraud, the oldest, based essentially upon the characteristic features of hair invasion by dermatophytes. Very much appreciated by clinical physicians, especially dermatologists, it still commands wide attention. (ii) that of Emmons is based on the characters of dermatophytes in culture. It is simple, includes only the genera *Trichophyton*, *Microsporum* and *Epidermophyton* and is widely used in the English speaking world; and (iii) the classification of Langeron and Milochevitch, slightly modified, is based, like that of Emmons, upon the morphology of dermatophytes in culture, and many European and South American experts use it.

1 Sabouraud's Classification of the Dermatophytes

This is summarized in the table taken from Sabouraud, *Les Teignes*, and is essentially based upon the characteristics of the pilar lesion. For example, all dermatophytes which invade hair by surrounding it with a sheath of spores in the form of mosaics are classed among the microsporums. This can in any case be produced by microsporums of the human type—these are pure microsporums—or by microsporums of animal origin—the neo microsporums. This first group is the most coherent even though the morphology in culture of the microsporums of animal origin differs greatly from that of the microsporums of human origin; these differences are, however, quantitative and not qualitative, the microsporums of animal origin forming a very great number of macroconidial and microconidial types, whereas these reproductive forms are rare, if not absent, in the human microsporums.

The second group, that of the trichophytons, is more complex. Sabouraud divides them into endothrix and ectothrix. The endothrix types are in turn subdivided into pure endothrix and neo endothrix, the ectothrix into microides and megaspores. The significance of these various terms has already been explained. The coherence of this group is much less than that of the microsporums and, if Sabouraud's basic feature of the classification, i.e. the pilar lesion, is adhered to, it is indeed hard to decide what resolves the grouping of these dermatophytes. The hair invaded by a microid or a megaspore differs completely from that invaded by a pure endothrix. The third group, that of the achorions, was based essentially on the formation of the scutule and comprised parasites of animal origin together with one human parasite, namely *Achorion schoenleinii*. It is to be recognized that, towards the end of his life, Sabouraud attached less importance to this small group. He had, perhaps more than some of his students, adhered to the idea of a botanical classification of the dermatophytes. Indeed he wrote (*Nouvelle Pratique Dermatologique*, 1936, p. 125): "Cases of favus of animal origin are rarely observed on man. Though scarce, they have great interest, for they will undoubtedly lead to a clarification of the subject, especially in relation to the unity of

the family of parasitic hyphomycetes and its position among the lower fungi and further (p 147) Bodin's *Achorion gypseum* is mycologically similar to the animal microsporum and on the evidence must from the botanical point of view be placed beside them

ARTIFICIAL KEY TO THE DERMATOPHYTES

I MICROSPORUM

- Large Microsporum [illegible]
- Microsporum [illegible] origin [illegible]

II TRICHOPHYTON

- Endothrix
  - [illegible]
- Ectothrix
  - [illegible]

III ACHORION

- [illegible]
- [illegible]

Value of Sabouraud's Classification

Sabouraud's classification is of considerable [illegible] been very serviceable and will doubtless continue to be [illegible] The underlying principle of the classification which is based upon the morphology of the dermatophyte fungi at the parasitic stage can [illegible] be accepted Parasitism is a convergent factor which leads different pathogens to adopt similar forms within the tissue These [illegible]

placed nder new conditions where they can underg full m rphological development may produce very diff rent form Examination of certain members of the chorion group renders th ery ob ious The type species of the group *Achorion schoe l* i i ha w th good reason been cla sified amongst the trichophytons *Achorion qu nckeanum* one of the agents ca sing mouse f us is lso a trichophyton (Vanbreuse hem 19 0) *Achorion gall nae* and *A gypse m* n dermat phytes which fall naturally into *Sabourard le* (*Microsporum*) of wh ch they have all the hara teristics Sabour ud opinion a t the s tematic position of the l tter ha already been g ven Pa sing t othe groups it w ll be appar t that *Trichophyton ferrugine m* which ca es m cro poric lesion of hair should ecording to Sabouraud be l d w th the m crosporum and that *Langeronia souda* which cau an endothrix ringworm should by th iew of the same author be a *Trichophyton* H wever morph logical studies which w hav carried out on this patho en have led us to regard it as the type of new genus (V nbreuseghem 19 0)

But perhaps the gravest objection to Sabouraud classification i that by t ery simplicity it run counter to inform t on on the morphology of dermat phytes in culture It is too easy t imagine all the relevant dat t be t hand once culture has been obtained from a pilar lesion of microsporic or endothri type This objection it m st be said is not directed against the proponent f the classificati Sabouraud alway aimed at perfect knowled of the morpholog f the dermatophytes wh h he de cribed and left us the be t il ble fi ure of their cultural morph lo y

In onclu on Saboura d l ssification take many fact int account but not all In our view it basis is erroneous We consider that the la sification of the dermatophytes must rest on the morpholo y in the media where they can de elop full nd not on the morph lo y of the para itic phase which because f con ergent phenomena is misleadin T a oid m sunderstandin it is to be added that if Sabouraud chose parasitic morpholog basis upon wh ch t establish his three great groups of dermatophytes he ch the morpholo y of the saprophytic phase t est blish the species

2 Emmons s Classification of the Dermatophytes

The l ssification propo l by Emmons (1934) is based upon the morphology of the dermatophytes in ulture It is epted by a con siderable number f expert mostly Anglo Saxon and wes it success apart from th meticulous b ervations upon which it rest t its simplicity and ts respect for the essential feature of Saboura d nomen lature This lassification writes Emmons is proposed in the hope that following the lines of natural relationship it will stabilize the nomenclature of the dermatophytes if it is ccepted It gi es back to three ancient genera (Emmons wrot t a time when bad impre sion had been reated by the revolutionary nomenclature propo ed by Ota and

Langeron 1923 and by Grigorakis 10) a mycological definition which up to a certain point seems to have been the intention of the creators of these names This classification has the great merit of simplicity and therein lies the chief reason for its enormous success However simplification is not everything and does not always lead to progress

The following is a summary of Emmons s classification as he himself put it forward

Dermatophytes These fungi are Hyphomycetes They are usually white but in some species show some shade of yellow pink violet or brown they reproduce by arthrospores by chlamydospores by single celled conidia which are subspherical or pear shaped to clavate with broad bases the base often being surrounded by a collar marking the point of attachment of the spore borne singly along the hyphae or in clusters on specialized conidiophores sessile or stipitate sometimes forming chains of two or three spores and measuring 5 to 4 by 3 to 6 microns They also reproduce by macroconidia which are clavate to spindle shaped or occasionally one celled but usually have from one to many cross walls and measure up to 40 by 160 microns in some species They grow in the skin and its appendages where they are present only as mycelia or arthrospores

Trichophyton Malmsten 184 The type species is *T tonsurans* Malmsten 1845 The mycelium is usually white but in some species it is yellow pink violet or brown The organisms reproduce in culture principally by conidia The macroconidia are clavat thin walled and sometimes wanting

Epidermophyton Sabouraud 1907 (not Lang 1879 or M gnin 1881) The type species is *Epidermophyton inguinale* Sabouraud 1907 which corresponds to *Epidermophyton floccosum* (Harz 1870) Langeron and Milochevitch The mycelium is usually y llow the organisms reproduce in culture by chlamydospores and by oval to egg shaped smooth thick walled macroconidia

Microsporum Gruby 1843 The type species is *M audouini* Gruby 1843 The mycelium is usually from white to brown the organism reproduces in culture principally by spindle shaped thick walled macroconidia and clavate conidia The former may be abortiv or f w in some species

Following thi series of short definition certain dermatophytes are listed under the three genera adopted by Emmon Th the genus *Trichophyton* includes all the small spored trichophyton (the microid) of Sabouraud under a single binomial *Trichophyton mentagrophyte*

Without going into all possible discussion of synonymy one is bound to wonder whether Emmons is right to include under a single genus both the classical and the microidal trichophytons of the same author Sabouraud We re against this for the following reasons—

( ) The microids form a well defined biological group They are above all agent of the suppurating ringworms represented by kerions and sycosis It is conceded that this fact alone must not be used to assign the microids to a separate group but it is fund mental taxonomic character

(*b*) The microid produce under cultural conditions morphological elements such as spirals pectinate hyphae and antler hyphae Even though these can appear in other genera and microsporums cultured in natural media can easily produce them it i nevertheless true to say that the microids are the only ones to prod ce them with particular abundance on the usual media

(*c*) The microconid (*aleuries*) f microids have particul r characteristics—

(1) They are very generally spherical and not pyriform or la ate like those of trichophytons

( ) They are disposed in clusters (*en grappe*) These are har teristic only of microids and are bsent from other dermatophyte though occasionally an early stage of their development may be bserved in certain strains of *Trichophyton rubrum*

(*d*) The macroconidia (*fuseaux*) of microids re quite different from those of trichophytons Emmons writes of the macroconidia of *Trichophyton mentagrophyte* "The macroconidium of *T mentagrophyte* is clavate spore which may be as much as twice the diameter of the branch bearing it and it may be of nearly uniform diameter or somewhat inflated toward the distal end It may ha e one or several septums The walls are thin and hyaline In some strains it is easy to find gradations between large clavate conidia and small macronconidia The macroconidia suggest differentiated chlamydospores somewhat more than the conidia In an occasional strain they re hardly more than hyphal tips which are differentiated by becoming several celled and are then detached bodily from the parent hypha They vary greatly in size Those which are one or tw celled may be 4 by 15 microns while the larger ones may reach 6 by 50 microns in size In our view this description would apply t the macroconidia of *Trichophytons sensu* Sabouraud (except for the microids) and *sensu* Langeron and Milochevitch which are usually rare and poorly developed *Trichophyton rubrum* is however an e ception to the rule This dermatophyte the study of which ought to be entirely repeated and the taxonomy of which is consequently in some doubt

(cf Vanbreu ghem 1949) is intermediate in morph l gy b t een the ctenomyces or microid and the trichophytons It forms conid a (*al urie*) of *Acladium* type pyriform but also often arran ed in mall clu ters

F 1
T lag l a l ((BV 140) T l cult l l
M cros b el t re l / // an l m or l m sm l j l
(400)

Further it m y form l und nt m croconid a which re lon t l nd tusing shaped

Langeron and Milochevitch (1930 p 488) wrot upon the m rphol gy of the ma rocondia f *Ctenomyces* H ma ro nidi of *Ct m t grophyt* re markedly longated nd l d l t s ll S l uraud ha de cribed their pyramidal form th walls uttin ff ll xt rn ll their ol tuse r button haped xtremity th ir len st lk ad l tly the ability to form onidi (*l e*) a phenom non th t h rn l n media

W l nes m m roc l f rm l l l f W l h tl t d ur l t m resul from l at l f l rpl l f l men ls in t us l out ultures l str a be l j f l on tituent el ment

They r much better developed on our (natural) medi than on classical media where they most ften present an ill formed ppearance either having the shape of shortborted macroconidia with the spect of hlamydo pore or resemblin thi k fil ment spindl shaped or drawn out t lon sept t ma s

W belie th t Emmons ha no justification on the ba of similarity of the morpholo y f the m roconidi for putting the trichophytons int the same g nu a the ancie t microid of Sabouraud

( ) There is yet further morphological l ff rence betw en *Ctenomyce* nd *Trichophyton* rising from the aerial mycelium which g es rise t the reproductiv structures In the trich phytons the m croconidia arise from aerial filaments a in the *Acladi m* type It is e ceptional to find microconidia in ny number arising on lateral branch at right angl t the aerial fil ment On the other hand it is usual in the ctenomyces or microid to encounter the l teral branch t right angles to the aerial filament and this branching sy tem yield the Lorraine Cross formation bearin the clusters of microconidia so charact ri tic of the species of this group Again *T rubrum* occupies an int rmediat position betw en the tenomyces and the trich phytons it aerial hyphae quite frequently forming Lorraine cro es which bea small cl sters f microconidia (al ie)

For the foreg in re sons w conside it undesirable to adopt the clas ification of the American mycolo ist Though based on consideration which merit approval in it attempts at simplific tion it confuse certain feat res of dermatophyt morphology wh h are v luable in lassifica tion

F nally it is sugg st l that adhere t t Emmons l result t ompare Fi 14 of Georg work (1948) on the f riform trichopl yton with Fi 5 f that f Georg and Maechling (1949) on a vari ty f *Tricho phyton mentagrophyte* It is impossible to disregard the considerable lifference bet een the ma roconidia and even the microconidia of the tw species and the necessity in ur iew to assign these tw dermatophytes t diff rent genera *Trichophyton* and *Ctenomyce* nd not to one genus as is done by these authors

3 Langeron Milochevitch and Vanbreuseghem s Classification of the Dermatophytes

It is not proposed t deal separat ly w th th cl ssification f *Lan eron* and Milochevitch as gi en by them in 1 30 for it only d ff rs from the present one in th inclusion by Vanbreuseghem f the genus *Langero ia* (19 0) Certain new details were introd ced in the first edition of M Langeron *Preci d Mycologie* This classification like th t of Emmons



F 13

[illegible] The matrix [illegible]



I 14

[illegible] H Marchling [illegible] permission [illegible])

is based upon the morphology of the dermatophytes in the saprophytic condition i e in culture [1]

(a) *Ctenomyces* Eidam 1880 Type *Ct mentagrophytes* (Ch Robin 1853) This genus includes the microid trichophytons of Sabouraud and corresponds to the single species that Emmons classes amongst the trichophytons i e *T mentagrophyte* It is characterized by microconidia

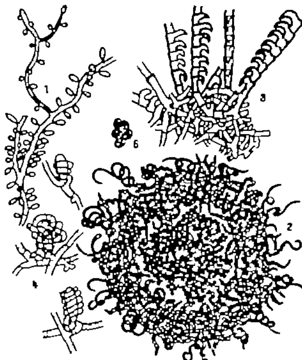


Fig I

Ct myces serratus I Mi roconi lopho ... ect on of matu pe th onum w th loosely woven ... l um of torul ... pectinate and ... l d hyphae ... nd m th ... west ... w ... mous hyphae and ase 3 Mycel um showing pectinate hyph ... with hooks 4 Beg nn ng of ... erith ec um formation (top shaped ascol ortes w th ... nt forming nodular bod es) ... Group of asci with ascospo ... (After Eidam)

Lange on and Milo he t h ha ... d ... gnated Sabou and ... micro ds by th ... name *Ct nomyces* ... Th ... old g ... name ... wrote Lang on in the first ed tion of the *P d ... de M l g* ... p 6 1 ... is unt nd l to d ... gnat ... the ancient tr chophyton micro d of Sab ... and because th y exh b t fully th morphology of *Ctenomyc* fully d ... loped bushy con d al str tures (m ... d) distaff shaped mac ... nd ... p nth ... al ornamentat on m th form of ... ll de eloped spirals borne p ... onaly ... filament with granula contents F t le pe ith eia have not yet be ob rved but there ... th ... b g nnings of fleecy pe thec ... milar to tho of the Gymn ... oal ... urround d by t nd l and antler l k ... filam ts Now pres ly

Fig. 16

[illegible] A. Mature perithecium [illegible] periodium of branching [illegible] B. [illegible] bearing asc[illegible] C. Asci and [illegible] (After [illegible])

Fig. [illegible]

Structure [illegible] 1 and 2 Initiation [illegible] terminal cell [illegible] and 4 swelling of [illegible] cell [illegible] Coiling [illegible] (After C. W. Emmons)

because [illegible] or [illegible] [illegible] ctenomyces. Th[illegible] observ[illegible] of Mat[illegible] [illegible] Langeron and Milochevitch [illegible] [illegible] (On the other hand [illegible] genus [illegible] Langeron [illegible] [illegible] microsp[illegible] [illegible] unnecessary [illegible] certain [illegible] [illegible] are necessary [illegible] [illegible] Langeron and Milochevitch [illegible]

hsq sed m l t rs or long hyphae m fel l and by di t ff haped macroconidia (*fu aur quenouill*) Spiral and antler like filament are found in cultures and are regarded a equi alent to the ppendages of perithec In this genus the nodular bodie that mul te the commence ment of a coqonium formation re clearest (Emmons 1934) Aerial filament g ving ri t conid in this g nus re branched at right gles and termin t with the formation f Lorraine Cross configurations Dermatophytes of this genu att k hair formin a heath f m ll spores h po ed m ll hu

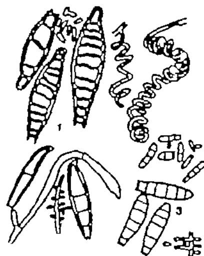
(*l*) *Sabouraudit*es Ot and Lan ron 1923 Langeron nd M l hevitch *mend* 1930 Type S a *lou* (Gruby 1843) This genu correspond t the genus *Microsporum* of Emmons and to S bouraud genus *Microsporum* t which are added cert in species S *gyp* nd S

F 1

l tl x l)) l pe of (*p*) (l l l l
hyphae) l (*pl p* ll m (*l g* l 1 3 l loq
m nt of j als an l ent l l hm nt of as mm trs 4 an l j ral
produces l l) rel l ped granula po ed filam t 6 j al
formed m dirare *ts* of naturally infected h k j an mo
bamble be sect on of tl j ral ed fl ment h w tl e fl t *g*
j l ne perpen l ul to tl of l j ral pectinat fl m nt
l l l j hm ft asexe ed l j ral l ft l an l l j r l
((ed j l (x o) ll rat l l l l) (Aft D Se an l
(rex)

gall nae whicl S bou ud placed in the genus *Achor* on be use like the agent f human favus they are ble t produce the ppear nc of scut l The *Sabourau lite* species ha microconidi of the *Aclad* m type and m pecies of animal origin ery numerous ma roconidia with lanceolat granulose wall Spirals ppear only ery ceptionally upon ordinary media but are easily obtained on natural media *Sabouraudites* specie in ade hair formin sheath of small rre ula spores n mosaic

(c) *Trichophyton* Malmsten 184 *sensu* Langeron and Milochevitch 1030 *nec* Ota and Langeron 19 3 Type *T tonsurans* Malmsten 184 This group has very little homogeneity and though treating it with respect we do not believe that it will retain its coherence Vanbreuseghem (1050) has already detached from it a species necessitating in his view the erection of a new genus *Langeronia* The morphology of *Trichophyton* cultures is very simple Certain species develop conidia copiously like the *Acladium* type along aerial hyphae The macroconidia occur exception



F 1)
Morphology of th *S* [illegible] *I* [illegible] macroconidia and micro conidia of *S* [illegible] coiled hyphae ([illegible]) 3 microconidia and macroconidia (*fm* [illegible]) of *S* [illegible] 4 microconidia and macroconidia of *S* [illegible] (After C W Emmons)

ally cigar or sausage shaped with smooth and thin wall having blunt extremities the base being lightly larger than the filament from which it arises Those species with glabrous colonies only exceptionally form conidia Spirals are not seen on ordinary media and only rarely appear upon natural media Certain species (*T tonsurans* *T sabouraudi* *T violaceum* *T rubrum*) produce lesion and [illegible] endothrix [illegible] by large spores arranged in regular files in the interior of the hair *Trichophyton ferrugineum* produces a microsporic appearance [illegible] that caused by the *Sabouraudites* species *T quinckeanum* causes the spontaneous appearance of scutula in mouse and man leaving the hair unaffected *T schoenleini* is the agent of human favus cause scutula and in the hair which it does not break the appearance [illegible] reduced to arthrospores The megaspored favif[illegible] cause an [illegible] ectothrix lesion with large spores in small [illegible] around the hair and certain species (*T megn* or *T roseum* of Sabouraud and *T* [illegible]

produce an endo ectothrix lesion characterized by large intra nd xtra pil r spore

E idently the genu is extrem ly heterogeneous and will undoubtedly be broken up arious attempts have been made to establish sub genera *Endotrichophyton* Lan eron 101 *Ectrophyton* Sabouraud 1938 and *Megalosporon* Sabouraud 1928

(*d*) *Langeronia* Vanbr useghem 10 0 Type *L soudan nsi* (Joyeux 191) Vanbreuseghem This genu is r pre ented by a single specie *I*

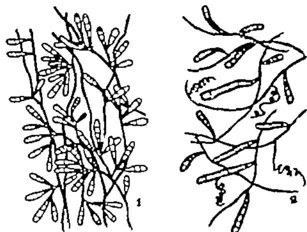


Fig 0

Morph olog cal l m nt of *Epi lermophyt n* cer l macro on l (*f* ar r) after th or g nal f gure of H urz (1870) ma ro on l an l co led hyph ae aft Lang on an l Milochevi t l (1930)

soudanense orr ponding t the older *Trichophyton soudanense* of Joyeux The egetat e mycelium w th quit short artic lations has marked tendency to form lateral branches growing opposit t the general direction of growth Upon these primary lateral branches arise secondary lat rals with the same general characters of the primary ones The repro ducti spores are mostly arthrospores which are easily d tached and may gi e rise in preparations to impressions of false branches The true conidia are rare and arranged in th *Acladium* manner The chlamydo spores which may be very bundant in old cultures are intercalary terminal or lateral Neither tendrils nor macroconidia are found

( ) *Epidermophyton* Lang 1870 Ota and Langeron 1923 Type *E floccosum* Harz 1870 *This genus is only represented by a single species* The reproducti forms are reduced t ery numerous club shaped macroconidia often bunched like bananas Langeron and Milochevitch have described tendrils in certain cultures but these organs re very rare *E floccosum* does not attack hair

THE PRINCIPAL DERMATOPHYTE

I Genus Ctenomyce

These comprise two group —

A Gypseus group with chalky colonies du to an enormou ac lation of microconidia—

Ctenomyce mentagrophyte	Ch Robin 18 3
Ctenomyces asteroides	Sabouraud 1909
Ctenomyces granulosu	Sabouraud 1908
Ctenomyces persicolor	Sabouraud 1910
Ctenomyce interdigitali	Priestley 191

B Niveus group with downy colonies—

Ctenomyces radian	Sabouraud 1909
Ctenomyce denticulata	Sabouraud 1910

II Genus Sabouraudite

Sabouraudite audouini	Gruby 1843	
Sabouraudites gypse	Bodin 1907	
= *S fulva*		Uriburu 1907
Sabouraudites canis	Bodin 190	
= *S felineu*		Fox and Blaxall 1896
= *S lanosus*		Sabouraud 1907
Sabouraudites gallina	Megnin 1881	
Saboura dit s langeron	Vanbreuseghem 1930	
Sabouraud tes ruralieri	Vanbreu eghem 19 1	

III Genus Trich phyton

Trichophyto ton ura	Malmst n 184	
= *T crateriforme*		Sabouraud 190
Trichophyton sabouraudi	R Blanchard 189	
= *T acum natum*		Bod n 190
Tr chophyton sulfureum	Fox 1908	
Trichophyton concentricum	R Bl nchard 189	
= *Endodermophyton concentricum*		Ca t ll ni 1911
= *E ndicum*		C st llan 1911
= *E tropical*		Ca t ll ni 1914
= *T roq tte*		da Fons a 19
Trichophyto qu nck anum	Zopf 1890	
Trichophyton violace m	Bodin 190	
= *T glab rum*		Bodin 1910
Trichophyton rubrum	Castellani 1909	
= *Epidermophyton rubrum*		Ca t ll ni 1909
= *T p purreum*		Bang 1910
= *T rubidum*		Priestley 1907
T m lticolor		de Magalhae nd N 19

— *T plaster form* — M cCarthy 19
— *T lanorowm* — MacCarthy 19
— *T coccineum* — Y hato 1936
— *T lilaceum* — Kawasaki 19 1
— *T A* — Hodges 19 1
— *T B* — *Hodges 19*
— *T salmoneum* — de M llo 19 1
— *T rubrum* var III — F ju 193
— *F pernet* — Cast llani 1910
— *T Kagawa* — Fujo 1931
— *T spod se* — Kat 19 6
— *T areolat m* — Negroni 1929

Trichophyton ferrugineum (Ota 19 1)
— *Microsporum f rrugineum* — Ot 1

Trichophyton schoenleini Lebert 1843
— *Achorion schoenle n*

Trichophyton album Sabouraud 1909
Trichophyton discoide Sabouraud 1909
Trichophyton megn n I Blanchard 189
— *T rosum* — Bodin 190
— *T roseum* — Sabouraud 1 10

Note It is necess ry to re rd s eral dev lopment forms and not species those described in 1936 by Langeron and B ra unde the names *T m locker ichi T pittal ju T brumpt T del men T inlice*

IV Genus Langeronia

Langeronia soudanense (J yeux 191)
— *Trichophyton soudanense* J yeux 191

V Genus Epidermophyton

Epidermophyton floccosum (Harz 1870
— *E cruris* — C stellani 190
— *E inguinal* — Sabouraud 1907
— *E clypeiforme* — M Carthy 19

Macroscopic Morphology of the Dermatophytes

It is irtually impossible to gi e a description of the dermatophytes in a work not devoted entirely to them Others howe er ha attempted this and profitable referen e may be made to Brumpt *Precis d Parasitologie* and Dodge *Medical Mycology* In identifying dermatophytes it is ad isable to consult the earliest de cription if there is any doubt as to the identity of particular strain isolated it is also ad isable to try to obtain fre h strain f the species in question better still if possible to send strains for confirmation to the author of the specie or to consult a mycologist with great experience of these pathogenic f n Unfortunately such authorities are extremely rare Research workers who

specialize in study of dermatophyt s are u ually well acquainted with the species in their region and as a general rule badly so with those of other regions We have a certain experience in the study of the dermatophyt of Central Afric and have isolated a great many strains of *Trichophyton ferrugineum* of *Langeronia soudanensis* and of *Sabouraudites langeron* We must confess that not a single week passes without our experiencing some difficulty in classifying one of them It is easy to imagine the difficulties in the way of anyone who only occasionally meets these species

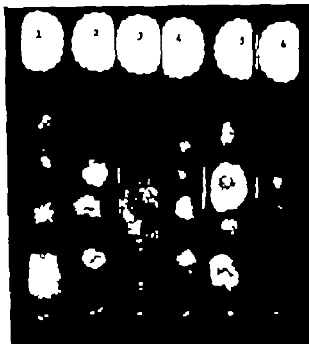
The identification of dermatophytes is rendered more difficult mainly for four reason

1 *There are several systems of classification in existence* This is neither a fundamental difficulty not in fact very important nor does it apply solely to dermatophytes it is for instance equally true of mycology helminthology or entomology Having made an adequate study of the microscopic morphology of a dermatophyte culture and of the pilar lesion which it produces—or does not produce—one would only exceptionally be unable to deal with it under the system of classification ad pted

The many synonyms constitute a second ol tacle to a simple classification Ota and Kawatzure had by 1933 enumerated 1 synonyms for *T rubrum* alone

3 Polymorphism in dermatophyt s a third diff ulty This poly morphism may appear in primary or sub culture An atypical strain of a well known dermatophyte may thus easily be regarded a a new species Vanbreuseghem (19 0) working with 130 strains of *T ferrugine m* isolated in the Belgian Congo wa able to distin ui h a whit variety besides the classical form further he demonstrated that e h f these two varieties yield f ur type of colony capable f i olation eithe simultaneously or separately *from the same pathologic l product and f* transformation from on type into another In view of th fact that on of these types was a d wny colony and another wa a colony k ly resembling that of *Trichophyton schoenle ni* it must be conceded that the identification of some *dermatophytes is mad part ularly difficult*

4 Pleomorphism of dermatophyt s a proce f irreversible tra f rmation of the initial strain whi h become progr ly cov red by white down made up f fine sterile mycelial filament The tran f rm tion i so radical that Sabouraud who first observed and described it long considered it to be a contamin tion or a he wrot a phenome of commensalism Th n ture of pleomorphi m i unknown it i h ever known that its pp arance is f voured by the use f sugars m l and retarded by ub culturing n non sugary or conserv ti n medi



F 1

1 P imary cult ure of *T ferru j* *lb* tra RV 1038 on per cent glu ose m d um aged 29 da upper 2 col es serpiginous and tl low rmost on downy

P imary culture of *T fe rug nea* stra RV 1104 aged 31 d y on per cent glucose med um Top t bottom serpig nous cerebroid l th ry and rebroi l show on th last be ng exa tly of tl *Acharion* *sel le* t pe

3 *T f rru g ne* strain RV 38 olat d 1 months ago and sub ultured m t mes Th colony on per cent glucose med um 3 day old It s of th l tl ery ty[an l s prec sely sam l m mo pl ology t st of *T fe g* solat l by Ota

4 *T ferrug nea* primary cultu of ra RV 1139 aged 36 da on per nt glu ose med um From top t bottom the f rst and second colonie are of th serpig nou typ the th d l atl ry th f urth leathery an l serp ginous

T f errug nea p imary ulture of stra RV 1165 on per cent glu ose med um aged 31 da At tl ntre colony of the l th ry type l ghtly downy t tl per ph ry A th bottom cer broid col ny

6 *T f rrug ne* p imary cultu of st in 1160 on per t glu med um aged 31 day Colony of the serp gin ou type with numerous satell te colon es

(Photog ph by R Saunder)

Raising the temperature to 37° C al o stimulate pleomorphism Certain workers including Sabouraud maintain that only some species of dermatophytes undergo pleomorphism Whatever the condition *Epidermophyton floccosum* rapidly undergoes pleomorphism Other workers including the present author believe *that all dermatophyte species may* undergo pleomorphism the phenomenon is not always so complet ly distinctive as in the examples described by Sabouraud and the whit down may not be so long nor so abundant but it occurrence seem indisputable The rapidity of the pleomorphic tran formation vari not only with the species but al o with the strain Pleomorphi m unfortunately overtakes most cultures in culture collections Undoubtedly these mycological centres are able to renew their strain and to supply a fresh typical sample to whoever requests a certain dermatophyte species but if some years have elapsed since the isolation of the requir l train one would receive only what the laboratory still retains r c mnants not at all resembling the original strain

Differ nt cla sifications confu ed nomenclature polymorphi m and pleomorphism such are the major obstacle to the re earch w rker I there any remedy? We see only one perhaps difficult to apply but which we believe would result in a clarification of our ideas in a conf d field and a quick reduction of multiple ynonym Those who isolate ringworm fungi sl ould send their strains—or pr f rably the product such a hair nails scale from which they have i olat d the dermat phytes—not t one laboratory but to five or ten all o er tl world and appointed by an authority on account of their knowl dge of the dermat phyte flora of the region in which they work Each laboratory would then arry out an independent ident fication the re ult f which would be communicated to the re earch work r either directly or through a central clearing ffice Some light would frequently enough emerge from the nsuing onfli t Though w harbour no illu ion as to the difficulty f applying this remedy we believe it to be the only ff ctiv one

Microscopic Morphology of the Dermatophytes

The morphology f dermat phyt in culture will be c l nsidered whether studied from t sed out fr gment in d uble strength l g l from culture on sl le in hanging drops or p on hair t im

The following point are important—

1 The g tati e mycelium
 The aeri l mycelium
3 The reproducti e stru ture mi r nidi (*al*) macroconi l (*fuseaux*) chl my lospore
4 Ornamented structures spiral (*p r*) n l hypha ti hyphae
 Nodular organ

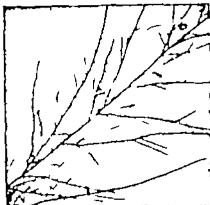


Fig. Cl ne / fre l 9l 1 lt aged 11 da l ery l ry (140)



Fig. 97 Same as Fig. l t t ntre (1 0)



Fig. 4 Sch al fre 9l 1 lture aged 3 day P rq l (140)



Fig. Same as Fig. 4 but t centre (1 0)



Fig. 6 T l epl ate a l rmal Slide culture aged 21 da l eriph ry (140)

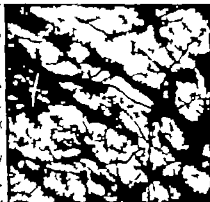


Fig. Same as Fig. f but t centre (1 0)



Fig. 28 *Epidermophyton floccosum* Slide culture aged — days Periphery (× 140)

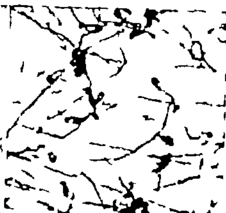


Fig. 29 Same as Fig. 28 ... centre (× 1 0)

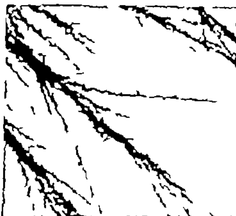


Fig. 30 *Langeronia soud ... nse* Slide cultur. aged 6 day. ... ry hery (140)

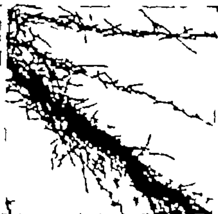


Fig. 31 Same as Fig. 30 ... centre (1 0)

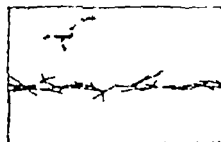
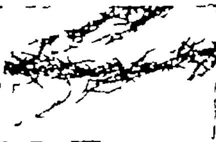


Fig. 3 *Langeron... ... brasus* Sl le culture aged (lay Detail of branched filam nt from he perip ery (800) *Inset* Liberated arthro pores forming images of microconi dia (800)



F 33 *L g ro ... l* Sl t cul ... aged d Centre (1 0)

The Vegetative Mycelium

The vegetative hyphae appear first in culture. Whatever the origin of the culture from pathological products—nail, hair, scales—or fragments of culture of macroconidia, microconidia, chlamydospores or of mycelium, the germination of these elements always results in the formation of a mycelial tube of 2 to 4 μ directed towards the periphery at the surface of the culture medium and which after travelling for 20 to 40 μ septates. The parts of the hyphae enclosed between two septa are called segments. Once formed the segment does not enlarge but it often gives rise to secondary hyphae which are mostly borne immediately behind the distal septum directed towards the periphery and make a more or less obtuse angle with the hyphae from which arose.

It happens occasionally that certain secondary hyphae instead of growing towards the periphery go backward. This is exceptional except in the case of the genus *Langeronia* where it is the rule.

The segment of the vegetative hyphae may swell at a short distance from the distal septum. This type of hypha which is more frequent in certain species than in others Sabouraud has given the name racquet hyphae. In yet other cases the vegetative hyphae bend in arcs of circles and protuberances appear on the convex side of each arc; to these Sabouraud has given the name pectinate hyphae. They are most clearly seen in the species *Sabouraudites ferrugineus* (Vanbreuseghem 1951).

The segments of the vegetative mycelium may fragment by the formation of transverse partitions; these fragments are arthrospores. When liberated from their parent segment the arthrospores may simulate macroconidia whose origin is quite different.

In certain dermatophytes quite long fragments of a segment may become isolated, divide into cells and present the appearance of macroconidia. This is particularly clear in certain strains of *Trichophyton rubrum*. Many workers relate these to the macroconidia which arise on the aerial mycelium. This is not to be accepted without reserve.

Upon emerging themselves into their support the filaments of the vegetative mycelium may wind up into a spiral; this is clearer in culture sections. These spirals have nothing in common with the spirals appearing in cultures of *Ctenomyces* and care must be taken to avoid confusion.

The Aerial Mycelium

This is characteristic of downy or powdery cultures. It arises on the vegetative mycelium behind a distal septum and coils slightly about itself at its point of origin. It is thinner than the vegetative mycelium and becomes shortly segmented. It may terminate abruptly or alternatively travel over long distances in a straight line. The aerial mycelium bears reproductive structures.

Reproductive Structures

The microconidia are [illegible] on either side of the aerial filament by the condensation of protoplasm within small pyriform or rounded excrescences. When these microconidia appear upon only one part or another of the



F 31

[illegible]

[illegible] lateral branches when they appear are at right angles [illegible] appearance. The [illegible] configurat[illegible] are in the form [illegible] Crosses co[v]ered with mi[cr]oc[o]nidi[a] forming grape-like m[illegible] extensive. This is seen in [illegible] and to [illegible]

The m[illegible] on [illegible] the [illegible]

ha e already been sufficiently described It is t be noted that the genus *Epidermophyton* which does not form microconidia prod ce macroconidi in clusters like bun hes of banana Those of *Sabouraudites* are lanceolate with thick and granular wall The *Trichophyton* have cigar shaped macroconidia w th fine walls Those of th *Ctenomyces* species ha e irregular w ll with a larg base and an obtuse extremity

Chlamydospores ari upon vegetative or aerial mycelia They are rounded cell of doubl e ontour which may be terminal lateral or inter l ry They re sometimes hains especially in old cultures

Ornamented Structures

I *Ctenomyces* and somet mes in other g nera when natural culture media are used there usu lly ppear spirals (coiled hyphae w th tight spirals) de tro or laev rot tory which rise from the end f thick and gran lose vegetativ hyphae Less frequently thick vegetativ hyphae may terminat with hook or antler shaped hyphae Da idson and Gre ory (1937) ha made a deta led and i teresting study of these form

Nodular Bodies

These ha be described by S bo raud connection w th *Ctenomyces* (*Trich phyton*) *lacticolor* They re regarded a rudimentary sexu l struct res (Emmons) They are lik m croconidia ha dense prot plasm c content and are t ghtly knotted They de lop in a similar fa hion to other form of reproduction S bouraud not ced that in old culture they may grow by putt ng out eget ti hyphae

Pleomorphism

Pleomorphi m of dermatophyt h be n define l (cf pr) an irreversible transformation of the init al strain which vers itself progressi ely with a whit down mark p f fine sterile mycelial filament nd some f the conditions governing it appearance ha been ind cated A l ttle amplification is desirable

Pleomorphism is irreversible A number of workers ha ttempted to bring bout the reversion of pleomorphic strain to thei initial morphology Acton and Dey (1934) claimed to ha chieved th by growing pleomorphic strains on feathers Lan eron and Milochevitch (1937) showed that this pparent succ ss w probably due to the f ct that they had used incompletely pleomorphi strain Cifurri and Pedaelli (1947) claim in certain cases to ha b erved a return to normal morphology by keepin pleomorphic strain pon natural media n the dark for

By grow ng pl omorph t ns of d rmatophyt (C / p cole an l *Ep d rmophyton flocco m*) upon ste ile so l Vanbreuseg m and Van Brussel have d monstrat d th ir rev rs on perfectly normal cultures non pl omo ph and rich in reproduct form If these b at one ar fied I found to apply to all D rmatophyt the dogma of he irrevers b l ty of pl omorph sm w ll ha rum its ou se Th first account ubl b l tl *C R Soc Biol* (195)

three years Hru ek (1936) failed to bring about reversion to the type culture by varying pH oxygen tension or by any other means He reported a curious and as yet unconfirmed phenomenon i e that pleo morphic strains of *Achorion gypseum* kept at 37 C change into culture of the fusiform type and when brought back to C the cultures revert to their usual pleomorphic type

Pleomorphic strains can be inoculated into animals (Langeron and Talice 1930) and into man (Hrusk 1930) The retro cultures yield pleomorphic colonies Langeron and Talice (1930) by inoculating the guinea pig with a pleomorphic strain of *Sabouraudite f lineus* observed that the pilar lesion was compo ed solely of intrapilar filament on the other hand they noticed that this inoculation immunized a guinea pig against a previous inoculation of a non pleomorphic strain of the same dermatophyte

Catanei (1933) summarizes as follow an important experiment upon pleomorphic strains I When th normal pilar le ion i of the endothrix type that which the pleomorphic culture produces is characterized by a reduction of parasitism The intrapilar element remain filamentous the formation of arthrospores being reduced or completely suppressed When the normal pilar lesion is of the ectothrix microsporic microid or mega pore type it is apparent that the characteristic sheath is no longer formed around the hair in the manner produced experimentally by pleomorphic culture

On the other hand the author like us con iders that the white d wn is not the only pleom rphic form He prove thi con clu ely by the fact that certain degenerate form in e le io in the hair identical with those produced by the classical pleomorphic form

The Law of Specificity of Dermatophytes

Much has been written about this law defined by Sabouraud (*L T pe* p 40) a the law of correspondence between the clini al ty f le ion and the parasite cau in it and it ha given ri e to vigorous di us ions How er expressed in the followin l ss ri id form The law f ificity of the dermatophyte states that th most highly d ff rentiated d rm to phytes u ually produc a reco nizabl le ion (Sabouraud in *Schw Medi Wochenschr*) it i admissible by very me a a g neral principl It is certain th t a scalp micro porum (*microsporie*) n l d sting ui hed from a trichophytia (*trichophytie*) th t a l sion i g nerally used by the spec *T crateri form* that a favic scutula is m tly caused by the species *T schoenlei n* that *Trichophyton rubrum* more than ny other dermatophyte is the ca f xt n i e and persist nt inf ctions f the glabrous kin that thi ame dermat phyt only exceptionally attack the scalp that t kelau (tinea imbricata ?) i used by only one d rmato phyt *T co centricum* that H bra s ec ema marginatum is i m t fre quently caused by *Epidermophyton floccosum T rubrum* or *T interdigital* that d rmatophytes f animal origin u lly pr l e purati

lesions whereas those of human origin are generally dry But this is a far one m y go *Sabouraudia audoui* S ca i *Trichophyton violaceum* re not alw y responsible for the same lesions *T violaceum* for example u ually produces a scalp ringworm but Majocchi in 1907 described it producing trichophytic gran loma and Teberno onboff in 1928 reported the occurrence of *T violaceum* in bony cavity Kaplan and Ra lsschek (1946) report l a ca f kerion cau d by *T schoe l* and could find only three more such case reported in the literature Hadida Marill nd Mourere described se of generalized favus on 16 year old Muslim girl in whom in l ment f the lymph nodes f the right inguinal region had indicated a picture f Nicolas Favre disease Haemoculture in this case had been posit e

E idently if the law of specificity f the dermat phytes applies to good many cases oft n it does not The c se of these riations is uncertain in some ca es it is due t a particular pathenogenicity of certain strains in others t a p rticul r receptivity on the part of certain patients

Symptomatology of the Dermatophytes

Dermatophyt symptomat lo y f which the reader can find excellent descriptions in almost any treatise on dermatophytes will not here be described at length The following may profit bly be consulted V l II of the *Nou ll Pratique Dermatologique* Paris Masson 1936 *A I tro duction to Medical Mycology* by Lewis nd Hopper 1948 and *M ual of Cl ical Mycology* 2nd Ed by Conant *et al* 1954

1 Dermatophyte Infections of the Scalp or Ringworm Proper

(*a*) The microsporias (*microsporie*) These di eases occur before puberty mostly upon children f school ag The lesion appears as a rounded plaque f erage diameter 4 to 6 cm t the level f which re found hairs broken 2 or 4 mm from the pilar orifice The hairs re surrounded by a whit sheath if they had been dipped into flour or fine sand after ha in been smeared with glue The microsporias of animal origin are often accompanied by a slight suppuration Th y are cured spontaneously t puberty

(*b*) The trichophyte infections (*trichophytie*) These are also found on children of school age and are characterized by small irregular plaques upon which are found short broken hairs sometimes so short that th y are red ced t black points bstructing the pilar orifice Their extraction is difficult and they are cured at puberty

( ) Favus This is acquired in infancy but may persist for life Near to non broken but lustreless hairs scutula are usually f und surrounding the pilar orifice These ha e a sulphur yellow colour and emit mouse like odour The lesions develop and lea deep scars which end in incurable baldness

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On the other hand, this author, like us, considers that the white down is not the only pleomorphic form. He proves this conclusively by the fact *that certain degenerate forms cause lesions in the hair identical with those* produced by the classical pleomorphic form.

The Law of Specificity of Dermatophytes

Much has been written about this law defined by Sabouraud (*Les Teignes*, p. 49) as the law of correspondence between the clinical type of a lesion and the parasite causing it, and it has given rise to vigorous discussion. However expressed in the following general form, "The law of specificity of the dermatophytes states that the most highly differentiated dermatophytes usually produce a recognizable lesion" (Sabouraud in *Schw. Med. Wochenschr.*), it is admissible by everyone as a general principle. It is certain that a scalp microsporon (*microsporie*) can be distinguished from a trichophytia (*trichophytie*); that a kerion is generally caused by the species *T. gypseum*; that a favus scutulum is in the main caused by the species *T. schoenleini*; that *Trichophyton rubrum* more than any other dermatophyte is the cause of extensive and persistent infections of the glabrous skin; that this same dermatophyte only exceptionally attacks the scalp; that tokelau (tinea imbricata) is caused by only one dermatophyte, *T. concentricum*; that Hebra's eczema marginatum is most frequently caused by *Epidermophyton floccosum*, *T. rubrum* ... *T. ... d g inlae* that dermatophytes of animal origin usually provoke suppurati

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(*d*) Kerions are rounded plaque more elevated suppurative and attack the head at any age The hair is spontaneously expelled from the



Fig 3
Larg pl t of micro p n m k gn

pilar orifice which mit pus Recovery is spontaneous Th k rions are usually cau d by micro l The hairs may be broken or inta t

2 Dermatophyte Infections of the Beard

These are also g nerally called k rions or para tu yc is They are produced by various dermatoph yt of whi h the microids are the most important They are found in adult men and possess the same a pect a the kerions of the scalp They cure spontaneously It is to be noted that the microbial yco re e pecially locali ed beneath the nostril p rtions

3 Dermatophyte Infections of the Glabrous Skin

Upon the glabrou kin may be found circinated l sion th centre of which ppe r to be health y whilst more l evat l edg se ly and vesiculo extend to the periphery Neighbouring ring may fuse These lesion commonly lled herpe circinatu or Saint Catharine whee l appear on ad ilt a w ll a children In our countries *S cana* seem t be the most fr quent agent

Under rtain cond tion favus may in ade th glabrou kin and form scutula a for the scalp

Kerion are frequently f und on gl brou kin They re ca sed by *Ctenomyce* or l mega pore *Trichophyton* Th se in contact with anim l





6 The Dermatophytids

Cutaneous or other lesions secondary to a pre-existing dermatophyte infection are named thus. They will be considered in the section on allergy.

Histopathology

There is little to be said on this subject, for the dermatophytes are primarily diseases which affect the superficial keratinized layer of the epidermis. However, the structure of favic scutula, the nature of favic alopecia, the trichophytic granulomas have evoked a great many studies which need not be considered here, for they make no essential contribution to the problem of the dermatophytes.

Treatment

Dermatophyte therapy varies according to whether the regions affected are the scalp, the skin or the nails. The following account is a broad summary of the treatment of these three regions when subject to dermatophyte infections.

1 Treatment of Scalp Ringworm As they are maintained by infection of the hair, the methods of treatment of scalp ringworm involve either depilation or alternatively destruction of the dermatophytes in the hair.

(a) Depilation

The first method ever to be used was mechanical removal of the hair by means of pincers or a wax cap. No longer used alone, this method is, however, used to improve depilation made by other means.

The second method is depilation by thallium acetate, devised by Sabouraud in 1897, but soon afterwards abandoned by him because of its dangers and especially on account of the introduction of depilation by means of X-rays. It has fallen into disrepute, which is perhaps regrettable.[1]

Thallium acetate administered *per os* induces hair fall after the seventh day. *Fall is completed from the sixteenth to the eighteenth day* and regrowth occurs after the third or fourth week. Alopecia due to the thallium does not extend to the eyelids and the inner region of the eyebrows. Early regrowth (perhaps due to the fact that small doses of thallium have a stimulating effect on regrowth of the hair, cf. Cooper and Engman, 1931) and also the danger of intoxication constitute the great objections to its use. Hairs reappearing after the third or fourth week stand a greater chance of being contaminated by hairs which have not yet fallen (after X-ray treatment regrowth occurs only after the second month).

[1] A recent [illegible] of Vart[illegible] [illegible] and is [illegible] of the Soc[illegible] [illegible] by the [illegible] which [illegible] [illegible] thallium acetate depilation [illegible] or the [illegible] after

Toxic ff ct due to thallium ect t manifest themselves by muscular and articular pain polyne ritc and by a temporary albuminuria This remedy cannot be administered after puberty because it cause glandular atrophy The optimum dose varies from 8 t 8 mg per kilo of weight and the do cann t be repeated before two months

Thallium wh ch can be i olated (Crookes 1861) from opper pyrites marcasit me blende is widely distributed in the plant kingdom e g in chicory tobacco w ne be troot and beechwood It i however usually obtained from lead chaml rs and furnace burning thalliferous pyrites Though t first mployed in the treatment of yphilis and exst tes it was soon abandoned becau of it cumulativ toxi eff cts

According to D vidson Gregory nd Birt it should be administered a follows children are w ghed naked for tw day running and a complete physical xamination nd rine t t made Chemically pure thallium acetat is a ery t llim powder which must be weighed twice and caref lly pl ced in a l belled bottle The correct dose—8 t 8 mg per kilo—is the lowest w ight in kilos multiplied by 8 or 8 When ready t be taken the thallium acetat is dissol ed in about 100 c c of sw etened water taking gre t are that the whole of the salt is dissolved Children over tw l years old and l those appearing to require a d more than 300 mg should not be subjected to this treatment H ving taken the med cine the child is put t bed f r 4 hours The head is sha ed and co ted with tincture of iodine three times a day After three days in hospital the child i sent home with tw caps one t be worn while the other is washed After l days the hair is w shed twice a day with soap According t these workers hair fall commences on the a erage towards the thirteenth day and is complete from the twentieth t the twenty fifth Inf cted hairs tend t fall later than healthy ones and regrowth commences before all the hairs ha e fallen The removal of the old hair must therefore be accomplished with great care and tincture of iodine must be con scientiously pplied

Though X ray depilation is the best method the thallium acetat method has certain value details for t use have been given fully because well administered thallium acetat is less dangerou than bad X ray pplication

The X ray technique cannot be acquired from book and when w ll pplied it gi es more certain results than thallium because hair fall occurs during the third or f urth week whilst the new growth does not appear before the second month There is th s time to bserve the hild head after hair fall and t remo e any infected hairs which have not been eliminated Remarkable results ha been btained at the Lailler school by skilful pplication f this method but the precautions to be taken for good results without danger can be learnt only by practical demonstration Elsewhere disastrous result hav been encountered such definitive baldness or therapeuti failure resulting either from insufficient dosage or bad distribution of the radiation

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Depilation by thallium acetate or X rays is essential and should be reserved for scalp ringworm of human origin such as *Sabouraudite audouini*. This matter will be further considered later. On the other hand ringworm of animal origin, e.g. *S. canis*, with their natural tendency to heal spontaneously, would appear to be more suitably treated by one of the following methods which expedite recovery.

(b) External Treatment of Scalp Ringworm

Though Sabouraud frequently denied that ringworm could be cured by the application of medicament because of the inaccessibility of the dermatophytes concerned, many attempts have been made along these lines during the last few years. Enthusiastic reports have given the impression that scalp ringworm is now only a trivial therapeutic problem. However, enthusiasm has often been far from general on account of frequent misinterpretation of successful result. Rivalier (1950) has noted recently that there are microsporias—even of human origin—which are spontaneously curable, and Kligman and Anderson (1951), in an article noteworthy in more than one respect, have reopened the whole question. From their experiences during a recent epidemic in the United States caused by *Microsporum audouini* they concluded that—

1. *Spontaneous cure occurs in a large number of people suffering from ringworm.*

2. In a large number of cases the infection is accompanied by an inflammatory reaction; if this sets in, healing follows.

3. *So called cures resulting from the local application of fungicide are* really spontaneous cures. This opinion was based on the observation of 190 cases in which the same percentage of cures (approx. 6. per cent) was obtained by using either the base alone (carbowax) or the fungicide (zinc ethylene bisdithiocarbamate).

One must therefore distinguish amongst the ringworm affections those which are spontaneously curable and those which are not. The latter, incapable of responding to local treatment, should be submitted to X ray treatment after a period of [illegible] to 1 month. As to the former, it remains to find out the extent to which local treatment expedites recovery. In any case it would seem that such a treatment would oppose the dissemination of the disease, even if it did not effect a cure.

Among the fungicides employed locally are antibiotics and chemicals.

A. Antibiotics

In 1946 Curry demonstrated the fungicidal and fungistatic action of tyrothricine *in vitro* upon dermatophytes. In France since July 1948 Catanei, Coudert and Cotte have attempted to treat ringworm caused by *M. audouini* with application of tyrothricine (1 mg. per g. of ointment) and obtained 41 recoveries (6[illegible] per cent) out of [illegible] cases in [illegible] to [illegible] days; in the remaining cases depilation with X rays was necessary. The correspondence of this with the [illegible] per cent of spontaneous recoveries of

Kligman and Anderson is noteworthy In August 1948 however Gate Coudert and Cotte reported further observ tions extending their work to the trichophyton infections and noting particularly good recovery from those of animal origin In 1949 Cate Coudert and Jehl confirmed these results and used daily application of a lotion containing 1 mg of tyro thricine per c c 70 per cent of acetone and 10 per cent of propylene glycol in alcohol at 70 C In widespread scalp ringworm however they preferred depilation by X ray

Moriame (1948) summarized the results of his experiments on the treatment of microsporic ringworm by local application of penicillin and they apparently do not differ from the above

B Chemical Remedies

These are so numerous that no attempt is here made to summarize them In practice they involve the association of a fungicidal or fungi static substance e g phenyl mercuric nitrate salicylanilide cupram monium hydroxide mixture of a propionate and a caprylate etc with penetrating base usually carbowax 1500 They gi similar results t those obtained with antibiotics Reiss and Winston (1949) have however obtained excellent results with podophyllin but C ldman has blamed this method for causing diffuse baldness (in Kligman and Anderson 19 1)

Conclusion There are tw types f scalp ringworm those which tend to heal spontaneously and those which do not The first are treated by the application of a local therapeuti which ppears to stimulat natural recovery and prevents the spread of the disease whilst the second are treated by submission to the depilatory action of X ray or possibly of thallium acetate

In our iew the greatest progress has resulted from the introduction of local therapeutic measures in so far as it is now recognized that there may be spontaneous recovery from certain types of ringworm disease which thus do not require the pplic tion of X rays

2 Treatment of Dermatophyte Infections of the Folds and the Glabrous Skin The dermatophyte infections f the glabrous skin lacking any inflammatory reaction of note may easily be cured by the pplication of 1 per cent iodized alcohol by Whitfield ointment the salicylic and benzoic acid content being carefully gauged ccording to the nature of the patient skin by Castellani s paint or by the pplication of one of the numerous remedies now available and usually containing unsaturated fatty acid

The following recipe (Castellani fuchsin) wa proposed by Castellani pour 10 c of an alcoholic solution saturated with basic fu hsin int 100 c of an aqueous solution of 5 per cent phenol Filter and add 1 g of boric acid Two hours later add 5 of acetone and after a further two hours 10 g of resorcinol Apply once or twice day Castellani particularly recommended this remedy for the treatment of tokelau in ery primitiv natives it use is difficult with civilized patient

The kerions caused by microid or megaspore have a natural tendency to heal. This is facilitated by the use of one or another fungicide. In a particularly resistant and extensive infection caused by *Ctenomyces asteroides* we had to resort to inoculation by *Trichophyton quinckeanum* a method we believe to have been used by Bruno Bloch. Eight days after this vaccination the patient was cured of a disease which had lasted two months and showed no improvement prior to the inoculation.

A genuine case of Hebra's eczema marginatum usually clears without difficulty by the application of one or other of the fungicides. The forms said to be resistant are mainly erythrasma. However the dermatophytic affections of this region caused by *T. rubrum* are said to defy therapeutic measures.

The treatment of dermatophyte infections of the feet or Athlete's foot is the subject of such an abundant literature that we deem it best to indicate our personal experience.

The hygiene of Athlete's foot should be appreciated. Whenever possible the wearing of sandals is recommended (cf. Nickerson, Irving and Melmer, 1945). The shoes and socks (the latter preferably of cotton) should be changed daily. The shoes may be disinfected by pouring commercial formalin diluted to 1/10 on to a wad of cotton wool this is placed in the shoe which is enclosed in a box or in wrapping paper for 24 hours. The shoe is then aired before use (cf. Weidman, Emmons, Hopkins and Lewis, 1945).

In the chronic form it may be adequate to powder the feet each morning with a proprietary powder or simply with 10 per cent boracic talcum powder. Weidman and Class (1948) have demonstrated the efficacy of this which has an activity comparable with that of the proprietary remedies.

In the vesiculous form a very hot foot bath in water to which an alkaline powder such as Borax, Bic. Na. and thymol 3 per cent has been added is recommended for eight days, night and morning, each immersion lasting 15 minutes. The foot bath is followed by careful drying with vigorous rubbing to remove the scale and open the vesicle. At night a proprietary ointment or simply Whitfield's ointment in which the concentration of the salicylic acid varies from 1 to 3 per cent and that of the benzoic acid from 5 to 10 per cent. Apparently it may be advisable to vary the material used on account of the formation of resistant strains (see Villanova and Casanovas, 1950). In the morning the pomade is removed by careful washing and a powder is applied for the day.

In the haemorrhagic form rest with limbs extended appears to be indispensable and in any case the patient is in most instances incapable of walking. The same treatment as for the vesiculous form should be applied but during the day ointment should be used. Foot baths with potassium permanganate (1: 4,000) are useful in keeping down secondary infection.

It is difficult to be certain whether Athlete's foot is cured and it

distinguish relapses from reinfections. We feel that treatment properly carried out for three months will bring about the disappearance of all clinical symptoms and that daily powdering prevent relapses in almost all cases.

3. Treatment of Dermatophyte Infections of the Nails. Of all dermatophyte infections onychomycoses are the most difficult to cure. The two main reasons for this are (i) the difficulty of reaching the parasite in the depth of the nail, (ii) the well known resistance of *Trichophyton rubrum*, which is one of the most frequent causes of ungual mycoses, to therapeutic agents.

The treatment of onychomycoses by surgical extraction has long been practised. This method always difficult to get the patient to agree to, can be recommended when only one or two nails are affected. Surgical traumatism is thus minimized and post operational treatments have some chance of successful application. Mere removal of the nail is not sufficient to effect a cure: local application of fungicides is necessary afterwards as long as there is any doubt about the healthy growth of the new nail.

Sabouraud in 1910 proposed the abrasion of the outer layers of the nail by means of a dental file. This instrument, a scalpel or a nail file must in any case plane away the nail before a fungicide may be applied. One of the most favoured of these is Whitfield's ointment in which the concentration of salicylic acid is increased to 40 per cent. It must be applied carefully, ensuring proper protection of the periungual tissues. The treatment must be kept up for six months to one year and the complete collaboration of the patient is necessary for good results.

Nickerson and White (1948) proposed the treatment of onychomycoses with ammoniacal silver nitrate, which appears to have the property of penetrating the keratin and acting as a fungicide. Out of 16 patients so treated these workers obtained 9 cures and 7 improvements. The number of applications necessary at the rate of one per week varies from 1 to 10. Franks and Sternberg (1950) by the same method reported 7 failures in onychomycosis due to *T. rubrum* and 7 successes in cases due to *C. albicans*. It has already been stated that only the true onychomycoses are caused by dermatophytes and that *Candida albicans* only causes perionyxis accompanied by trophic lesions of the nail. In two cases of onychomycosis due to *T. rubrum* we have tried the method of Nickerson and White without success.

Thus the best method of treating onychomycoses seems to be abrasion of the nail followed by the application of a keratolytic and fungicidal substance.

Prognosis

The dermatophyte affections are of a minor character, many of them healing spontaneously. Favus, which is rare, is the most serious because of its duration and the alopecia which it causes. The kerions and the parasitic sycoses are painful but not serious. Lesions of the nails produced

by dermatophytes are unsightly and when the nail of the hand are involved they resist most methods of treatment Athlete s foot which is benign can cause serious loss in man power on account of the number of individuals it attack

Differential Diagnosis

A considerable number of cutaneous affections may be confused with those caused by Dermatophytes Scalp ringworm and tokelau are the easiest dermatophyte infections to diagnose after some slight experience However even favus of the scalp may be difficult to diagnose in view of the fact that there are forms of favus without scutula which have been well described by Sabouraud and the number of which is probably increasing Fyckmans and Vanbreu eghem (19 1) called them afavic favus Mistakes are made often in connexion with the dermatophyte infections of the nails and folds of the skin In our experience diagnosis of dermatophyte infection is often based upon lesions not of a dermatophyte type and the real dermatophyte diseases are often ignored even by the most advanced observers

Diagnosis

Five different techniques are used for diagnosing dermatophyte infections each with its own particular value These involve microscopic examination (of hair scales and nails) culture experimental inoculation culture upon isolated hairs and examination under Wood s light

1 Microscopic Examination For microscopic examination to be of value the sampling must first be well carried out the sampling being almost more important than the examination it lf

(a) Examination of the Hair

It is easy enough to take with forceps a few hairs broken at the level of a patch of microsporia but this procedure is more difficult with trichophyte infections where the hairs broken off at the level of the pilar orifice are almost impossible to seize *It is better to rub the suspected* patch with the forceps mount the debris n lak t a ut ith needl and select out suspected fragments with the help of a lens A fragment mounted in chloral lactophenol under co r lip is xamined und critical illumination on the microscope

In scalp favus diagnosis i a y if there i scutula one m h s taken with two zers and ru hed in a petri dish A fragment of the scutul placed in a drop of chloral lactophenol will show numerous rtl r j on *of irregular shapes The hair which i th centre of th scutula* xamin d imilarly t investigat the covering filament In the c e of f u without scutula it is usually best to examine the patient with Wood light and to take specimen of fluorescent hair at the time of the examination

The use of freshly prepared 10 per cent n tr p st d 1 t for the

xamination of hairs is not to be recommended This alters the disposition of the mycelium in and round the hair t much whereas hloral lact phenol lea es the filaments intact Certain mycologi ts however prefer to use pot sh for the xamin tion of fa se hair bec use this is the only



F 38

M cel l filament from scale pass m h Atl l t foot (s do s f rm) Culture y l led (gra ed q ted (tra 11X 10 4) Prep t potash (0)

mean of causing air bubbles t appear in th hair and this is thought to be of great alue in diagnosis

Needless t say reproductiv structure such micro or macro onidia are never found in the hair nor in scales and nails This remark would ha been omitted had not recent American work (Appel and Ansel 1949) affirmed that macroconidia (*f* *waux*) had been found in infected hair The structures in question were not macroconidia but epithelial cells of the pilar f llicle wh ch liberated with the hair at the time of it evulsion simulat rather poorly the macroconidia f *Sabouraud le* Work done by Ajello (19 1) ha already corrected this mistake

(*b*) **Examination of Scales**

Scales are rem ed w th forc ps If they are too small for this the epidermis is scraped with either the blade of an old scalpel or with a

vaccinating stylet over a slide sterilized by heating in a flame. When there are blisters the top of one is torn away or removed with scissors. In contrast with hairs which must be examined in chloral lactophenol scales may be examined in potash after slight warming. Microscopic examination using a high powered eyepiece and a low powered objective enables the moderately practised eye to scan the preparation rapidly and recognize the possible presence of branching mycelial filaments sometimes reduced to arthrospores which provides the diagnosis. There are two possible sources of error—

1 Contamination of the scales by saprophytic *Penicillium* or *Aspergillus* species mycelial filaments of which may be present. These are fairly easy to identify because their diameter often varies considerably in the same preparation; moreover in cases of contamination the easily identified fructifications of *Aspergillus* or *Penicillium* are often found.

2 The *Mosaic fungus*. There is as yet no general agreement as to the exact significance of these curious forms which may be mistaken for the mycelium of dermatophytes. However the shapes of the pseudo mycelia are more geometrical than those of the real mycelium, the segments of the false mycelium of mosaic fungi often having sharp or angular sections at their extremities.

Examination of scales in chloral lactophenol is not to be recommended for the turbidity of the preparation obscures the mycelial filaments.

(c) Examination of Nails

Nails should be examined in a freshly prepared 30 per cent solution of caustic potash. As with scales chloral lactophenol does not clear them sufficiently. Good sampling is essential with the aid of scissors, scalpel or razor blade and the part of the nail really attacked must be removed. In the symptomatology it has been pointed out that the surface of the nail may remain intact when the nail was internally affected. Thus the external region of the nail must be removed to obtain the diseased part. Bad sampling is undoubtedly responsible for many microscopic examinations appearing to be negative when from the clinical point of view the diagnosis of onychomycosis is evident (cf Dostrovsky, Raubitschek and Sagher 1955). It must be added that this clinical diagnosis is insufficient.

2 **Cultures** Cultures should be made on Sabouraud medium with per cent glucose as modified by Langeron. To obtain primary cultures more easily it is useful to add penicillin to the medium according to Vanbreuseghem technique (1950). As with the microscopic examination it is essential to commence with samples correctly obtained and to carry out several inoculations in order to obtain a positive culture. Hairs will always give cultures, scales less easily and nails less readily still. Commencing with 61 samples of nails which had given a positive result on microscopic examination Dostrovsky, Raubitschek and Sagher (1955) obtained only 11 cultures of dermatophytes. This is an extreme case we

ea. ly obtain 60 per cent po itive results from the appropriate samples and the percentage would be better still if w could repeat the sampling or had the samples more bundantly a ailable Weidman and Class (1948) who btained 30 per cent po iti results by cult ring samples from cases of Athlet foot insi t upon the need to repe t the cultures

Quit number of authors empha ize the alue of wa hing scales with alcohol before proceeding with the culturing Apart from cleaning the lesions with alcohol or ether at the time of sampling w ha ne er found that there was any need to do this It however noteworthy that those who work with tokelau g Castellani Ari Le o and Coto insist upon the procedure

In our view the one esse tial is to make number of cultures Whereas it i u ually sufficient to inoculat single tube t three point order t isolat dermatophyte from hair in the case of scales or nails it i often necessary t deal with fiv or ten tubes in this way between 1 and 30 inoculations t obtain a positi result

Three small points in connexion with the study f dermatophytes m t here be dealt with namely antagoni m between bacteria and dermatophytes antagonism of dermatophytes between them el es and finally the problem of mixed infection

( ) Antagonism between Bacteria and Dermatophytes

The question at is ue is whether bacteria xert a stimulating or an inhibitory action on the growth of dermatophytes Since the experimental result of arious workers are so inconclu e part of the problem clearly eludes us In general w y however it is clear that when samples for ulture re heavily contaminated with bacteria olation of the dermatophytes becomes difficult Indirect evidence for this is found in the fact that inoculations upon Sabouraud s medium with penicillin often gi more reliable results than tho done on media without penicillin

In 19 0 Catanei concluded from numerou experiments that staphylococci fa our the development of *T schoenl* H wrot however that the de lopment of the fungus is all the greater as that of the microbe is limited On the other hand Baudet (193) btained more bundant and more downy cultures of fa iform trichophytons upon an agar medium based upon a staphylococcus culture in ordinary broth which had pre ously been sterilized by heat

Against these bserv tions supporting the iew that microbial action stimulates the developme t of dermatophytes are opposed the results of Falchi on the one hand and of Vanbreuseghem on the other Falchi (1934) inoculated Sabouraud medium incubated t 37 C with pyocyanic bacillus a staphylococcus colibacillus a Monilia and a member of the Torulopsidaceae After four day he inoculated int the centre of the culture thu btained some *T gypseum niveum* *T violace m* *M lanosum* or *A schoenlei* respecti ely In all cases there was an inhibitory action the most resistant fungus being *M lanosum* and the colibacillus

being the least active On the other hand filtrates from cultures of the staphylococcus the colibacillus the pyocyanic bacillus and the Monilia added to Sabouraud's medium did not prevent the growth of the dermatophytes but rather seemed to favour it In order to explain the inhibitory mechanism Falchi concluded that it involved a direct action of the microbial agents upon the fungi by means of toxins or diastatic action

In order to simplify the problem Vanbreuseghem (1948) limited it to study of the effect of *Staphylococcus aureus* upon *Trichophyton schoenleini* and concluded that (i) *Staphylococcus aureus* exert an inhibitory action upon the growth of cultures of *T schoenleini* upon conservation media (ii) the inhibitory power varies according to the strains of staphylococci and of *T schoenleini* employed (iii) the inhibitory power is found neither in heat sterilized cultures nor in extract or filtrates (iv) filtrates from staphylococcus cultures do not exercise a favourable influence upon the growth of *T schoenleini*

It is thus evident that the problem of this particular type of antagonism *in vitro* is far from solution Other somewhat different studies have been carried out with the aim of using the antifungal power of certain bacteria e g *Bacillus subtilis* (Lewis and Hopper 1948) and the pyocyanic bacillus (Balabanoff 1947)

The antimicrobial activity of the dermatophytes appears in general to be of little consequence Ciferri (1948) who studied it in relation to staphylococci attributed a maximum activity to *Achorion violaceum* a medium activity to *E interdigitale E rubrum E floccosum* and *T gypseum* a little marked activity to *E inguinale* and *A gypseum* a small activity to *T asteroide* and *A gallinae* and doubtful activity to *M audouini* and *A schoenleini*

(*b*) **Antagonism between Dermatophyte Colonies**

This small problem is difficult to summarize because it has so far attracted the attention of research workers so little and the facts so far reported are disparate enough One may begin with the following fact observed on many occasions and easy to repeat if a dermatophyte such as *T crateriforme* or *Sabouraudites canis* (cf Vanbreuseghem and Moriame 1949) is *grown on an agar slant* at two points separated by 1 cm toward the middle of the culture medium and half way up the agar slope it will be seen that whereas at first two colonies circular in form will appear as soon as they reach a diameter of 4 to mm the growth will slow down where the edges of the colonies approach one another whilst it increases elsewhere Between the two colonies there persists a narrow band which neither colony will cross and it seems that each colony continues to develop in the direction where it finds most free space in front of it

If instead of only two inoculations one is made every 10 or 1 mm down the whole length of the agar slant each colony though tending to form a perfect circle will have its growth stopped by the two neighbouring

colonies and only those situated at the ends of the row will be able to develop fully towards the free agar

These essential facts form a starting point for more extensive observation

If instead of one dermatophyte different species are used various results may be obtained as has been shown by Dostrovsky and Raubitschek (1947) These authors consider that *T gypseum* and *T interdigitale* do not inhibit one another and that *T schoenleinii* and *T violaceum* do exert an inhibitory action on one another but not on *T purpureum* and that *Epidermophyton inguinale* prevents the growth of other dermatophytes (with the exception of *T purpureum*) as soon as its colony reaches and surrounds them

Spada (1949) studied the effect of broth culture filtrates of dermatophytes upon the development of other dermatophytes He concludes that (i) such filtrates are fungistatic towards dermatophytes (ii) the fungistatic power is proportional to the age of the broth culture of the dermatophyte which yielded the filtrate (iii) all these filtrates are not active towards all strains and certain filtrates have a much wider spectrum of activity than others and (iv) the filtrate from one species is active towards several strains of the same species but not towards the one that yielded the filtrate

It would seem that the fungistatic action of filtrates need not necessarily be related to the antagonism manifested by certain species This aspect requires much more study before any general conclusion can be drawn

(c) **Mixed Infections**

The culture of samples from a diseased region usually results in the isolation of only one dermatophyte species However a few authors have drawn attention to the isolation from the same lesion of several (usually two) species of dermatophytes see Catanei (1933) Muskatblitt (1941) Francis and Rosenbaum (1950) Loewenthal (1948) Vanbreuseghem and Moreame (1948) Milochevitch (1938) Cawley and Horne (1949) Tanessa (1949) Blank (1951 1951b) and Sabouraud himself (1910)

The number of published instances probably does not reach a hundred and the causes of the effect are quite obscure Before commenting upon the rarity of these mixed infections information is required as to whether their real frequency which is unknown is less than that of possible infections by each of the isolates in other words out of 100 individuals with favus how many would have been infected by the *T violaceum* found on one of them in association with *T schoenleinii* if none had had the favus infection In the absence of data no answer to this question is forthcoming yet

3 Experimental Inoculation Inoculation of dermatophytes into laboratory animals is rarely used for the identification of the fungus but usually to study immunity and the nature of the pilar lesion

The guinea pig is the preferred animal and has been the m t u ed The disease develops in it 1 days after an incubation period of t 10 day 1e there i little to ee for a month after the inoculation All dermatophyte species do not give the same results Some such a the



F 3
C m 1 k inoculat d h f t e g per color Le ion t tenth 1 aft inocul t

Ctenomyce are always inoculat d succe fully whil t oth rs g incon sistent result or failure Inoculation f spe with glabrou colonies rarely profitable

Inoculation techniques vary l ttle All aim at n int mat ntact betw n the kin f tl guinea pig and the derm tophyt for the in ul tion to have some hance of ucces Sabouraud adv cated the intro duction of a para itize l hair i to a sm ll w und in the skin f tl g ne pig or by rubbing a cru hed ulture over sha l kin Tal e Morillo a l Calzada (1931) ampli hed the part ularly l fl cult inocul t on f *T ferrug neum* into the guinea pig by means f the scab produced by ervocautery Our wn pref rence is for R v l r t In (1 1)

which is simple and which we found effecti e be dal According to I bc A pul erized portion of a fully d loped (3 week) culture on S bouraud agar is removed and mi ed in mortar with small quantity of honey The virulent paste is applied to a healthy gu nea pig over a piece of skin with the dimensions of a five franc piec nd simply cut with the scissors gl ss rod is the only instrument ne ary for this application The resultant infection is constant nd I have had no failure amongst 4 guinea pi so inocul ted It must be noted howe er that this consistency of I ivalier s result w due t the fact that he worked with *Ctenomyce gra los* and all other sp cies do not work so well

The age of the culture used for inoculation seems to be of some importance thou h no general data is ail ble on this After f ilure in our attempt t inocul te guinea pig with young cultures of *Langeronia soudanensis* (Vanbreuseghem 19 0) we recalled Catanei success in inoculating thi dermatophyte nto guinea pig nd Algerian monkey by using ld cultures Repetition f our experiments with old cultures transformed failure into success

The effect of inoculation of the guinea p g with a dermatophyt are pparent from the seventh to the tenth d y when erythema and desquamation are evident Examination f the scales re eals mycelial filament and littl l ter the hairs re in aded These fall eventually Towards the third or fourth week the only sign of the inoculation is a gl brous plaque over which the hair soon grow again

4 Culture of Dermatophytes *in vitro* on Isolated Hairs According to Vanbreuseghem (1949) this cult re method permit the fact to be established independently f morpholo ical ch racters that the sol t is indeed dermatophyt From t 10 day after the introduction f a suspected growth upon hair the destruction of the hair by the fungu becomes pparent either by destruction of the cortex toward the centre or by the formation of perforation organs which e ter the hair and di ide int many segment Vanbreuseghem in applying this technique t the study of numerous derm tophyt species h s hown th t most f them can produc such lesions and that they stand lone among t the fungi in this respect Th a new diagnostic method is ailable and a useful technique for studying the microsc p morph logy f the fungi

5 Wood s Light This type f light result when ltra iolet ray f elength 3 6 0 Å approximately pass through glass filter—Wood filter—containing nickel xide I the dark this radiation causes various substances to fluoresce Margarot and Devèze disco ered that h m fected by ringworm fluoresces in Wood light This is consequently sed in diagnosis in following the treatment f patient and in the detection of sources f ontamination

When a hild s head affected by microsporia is xamined in Wood light the patches of *teigne tondante* exhibit a greenish fluorescence Infected hairs isolated amongst healthy ones or which ha fallen on the clothes are easily recognized

of the *urticaria* type or a retarded reaction of a tuberculin type. This reaction appears immediately after the injection. It is less frequent than the retarded reaction which commences after 24 hours and takes the form of a papula surrounded by an erythematous zone sometimes reaching 10 cm in diameter; the reaction reaches its maximum toward the second or third day and usually disappears toward the fourth or fifth day, sometimes later, leaving a darkish pigmentation and a slight desquamation. This local reaction may be accompanied by a general one, a moderate temperature, discomfort, polynuclear neutrophilia and relative leucopenia, and a regional reaction (inflammatory conditions at the site of the mycosis). In non-sensitive individuals the injection of trichophytin produces a lymphocytosis (cf. Cavallero).

All dermatophytes do not sensitize equally individuals with favus, for example, even when the attack is very serious, show no reaction. Strong sensitization accompanies dermatophyte of animal origin. *Trichophyton rubrum* very little, whilst *Epidermophyton floccosum* is known to be one of the most active sensitizers.

The trichophytin reaction has only one group specificity, i.e. it can be induced by trichophytin prepared from any dermatophyte in a person affected by a very different dermatophyte. Its diagnostic value is thus very limited. It is positive in a certain number of individuals apparently free from dermatophyte infections. Muskatblitt and Director (1931) found it to be positive in 181 (60.3 per cent) out of 300 clinically attacked by a dermatophyte infection and in only 2 (4 per cent) out of 50 apparently unaffected individuals. It is generally admitted that there is a higher percentage of positive reaction in the control experiment; the result of American workers are in any case corrected by the fact that the percentage of positive reactors reaches 73.3 per cent in cases where clinical diagnosis was *confirmed by microscopic examination or culture, and falls to 4* per cent in those cases where this examination was negative.

A positive reaction may be found ten years after the infection which caused it.

Sensitivity to trichophytin can be passively transmitted by injecting serum from a positive reactor into the skin of a negative reactor (Prausnitz-Kustner phenomenon). *The reaction would be* automatic in using the serum of an individual giving an immediate reaction of the urticaria type. According to Jillson and Huppert (1949) the retarded reaction—tuberculin type—*is the first to appear, made evident by the* tissular antibodies; the precocious reaction—urticarian type—*appears later and is rendered obvious by the circulating antibodies.*

Once a source of dermatophyte infection is installed in a part of an organism, it can move for a certain distance but besides the lesion produced by the immediate extension of the parasite certain others to which Bruno Bloch gave the name trichophytids appear at a distance. Usually appearing on the tenth day of the infection or later trichophytids

correspond to a st te of sensiti ity induced by trichophytin in fact it is agreed that they appear only in positive reactors

Trichophytids arise abruptly and exhibit a symmetrical distribution They have a variable appearance knotted erythema scarlatiniform exanthema polymorph c erythema erythemato pustular eruption dyshidro is lichen Injection of trichophyt n in a person with tricho phytid produces t the position of the injection trichophytids with the same clinical a pect as the pre existing ones

The exact cause of trichophytids is still unknown It is thought that they may ari through the pa age of the fungus through the blood or of sensitising sub tances produced in the centre of dermatophyt infection The symmetrical disposition of the trichophytids suggest that they originat from the blood The fact that in certain cases t ha proved possible to i olat the fungus from the bloodstream of patients with trichophytid favours the parasitic nature of their formation On the other hand the existence of a toxin in the blood has ne er been demonstrated (Peck 1930) Certain writers hold that trichophytids may arise by the ontact of healthy but sensitized skin with the seat of the infection but the characteristic symmetry of the lesions opposes this view

Trichophytid are usually sterile and nearly all attempt to culture from them hav failed Moreov r it must be admitted that the fact that lesions yield cultures is proof that they cannot be classed a trichophytids

The trichophytid concept ha rapidly become very popular From there it ha been easy to pass to that of ids in general and the microbid in particular t desi nate all le ions of an allergic nature appearing t a distance from a seat of inf ction responsi le for them According to Peck (1940) the following are the criteria which permit a diagnosis of microbid —

(i) The organism re ponsible must be demonstrated in what is considered to be a cli ical manif station of the disease e g lesion an Athlete s foot

(ii) The organism isolat d must be pathogenic This however is not ab olut ly ential

(iii) A reaction simil ir to th t of tuberculin or trichophytin must be detectable

(iv) What is regarded a a m crobid must frequently company the primary lesion

( ) The same organism a is isolated from the primary le ion must be obtainable by haemoculture (It is feared th t this criterion is however only seldom ertified or verifiable)

(i) The microbids must ppear after the primary lesion

(ii) The microbids are usually sterile

(ii) The diagnosis of id is support d by—

( ) Their appearance in the form of multiple disseminated elements

(*b*) a tendency toward the asymmetrical disposition of the element

(*c*) a tendency towards spontaneous recovery after healing of the primary centre of infection

From this idea of cutaneous trichophytid there is a tendency to pass to that of vascular lesion. Even though the nature of the former seems to be readily acceptable much has still to be done before there can be any conviction about the latter. Peck (1930) divided the trichophytid into four groups—

I Epidermic trichophytid (attacking the epidermis)

(*a*) Eczematoid (dyshidrotic)
(*b*) Lichenoid
(*c*) Parakeratotic
(*d*) Psoriasiform

II Cutaneous trichophytid (particularly attacking the papillary body)

A Diffuse forms—

(*a*) Scarlatiniform exanthemas and enanthema
(*b*) Erythrodermic

B Circumscribed and disseminate forms—

(*a*) Follicular localizations usually lichenoid
(*b*) Localizations not exclusively follicular—maculose papulose and even exudative eruptions
(*c*) Erysipeloid forms

III Subcutaneous trichophytid (hypodermic nodules of knotted erythema type)

(*a*) Acute form tending to heal
(*b*) Chronic form tending to increase

IV Vascular trichophytids

(*a*) Venous *phlebitis migrans*
(*b*) Capillary urticaria
(*c*) Purpura

The idea of vascular trichophytid seems to lack any firm support. Peck however goes as far as to affirm having seen phlebitiform rises which he attributed to vascular trichophytid. Certain observations upon the causal relationships between the dermatophyte infection and Thrombo Angeitis Obliterans have either been forgotten or reported with very little confidence. They may usefully be recalled because of their theoretical interest and because they merit verification. Thompson (1911) was the first to attempt to establish a relationship between Athlete's foot and Thrombo Angeitis Obliterans (T O). At almost the same time (1911)

Meyer Naslo published his observations of 30 patients with T O 28 (93 per cent) were suffering from Athlete foot and in 20 of these the dermatophyte infection was imported Observation of 30 control cases revealed the existence f dermatophyte inf ctions in ... (73 per cent) of wh ch 9 were of serious nature Cutaneous reaction with trichophytin was positive in 4 patients suff ring from T O (80 per cent) and notably m patient clinically free from Athlete foot whereas only 6 of the controls (20 per cent) reacted t trichophytin Ten patients were observed during acute attack of T O the attack w s preceded by aggra ation of the Athlet foot in 7 of them Meyer Naslo vainly attempt to explain the predominance f T O in males though femal are equally susceptibl t Athlete s foot on the grounds that this disease is usually less serious in women and less frequently accompanied by a positiv trichophytin reaction Rei and Graham (1946) using technique devised by Reiss (1944) were unable t detect ocular lesion in castrated rabbits infected by T purpureum for 1½ years More recently Holman (1947) claimed to ha btained interesting re ult by treating two case of T O with trichophytin injections

So far as we know the problem rests t thi point it would not ha been presented had not certain clin cal f cts recently bserved by us given them a possible alue

9 *Therapeutic Utilisation of Trichophytin* Cutaneous sensitivity towards the injection of trichophytin only develops if dermatophytes parasitise the skin (Sulzberger 1940) it does not ppear even if the dermatophyte is found in deeply seated organs Rivalier (1929) observed in the guinea pig the formation of a oluminous sub cutaneo bsces after inoculation by a li ing *Trichophyton* without any kind f resultant immunity or allergy Rivalier ha on the other hand attempted unsu cessfully to desensitise guinea pigs by means of intradermal injections of trichophytin This worker (1936) thus considers the therapeutic action of trichophytin to be illusory

These facts and other analogous ones ha discredited trichophytin the possessor f antigenic properties and ha e caused the substance to be regarded only a reaction

It is however to be noted that repeated injections f trich phytin terminated without accompanying cutaneous reactions even if at the time of the first injections they ind ced considerable reactions The con erse would not hold good and it would appear to be impossible to sensitise man or animals to trichophytin by repeated injection of th substance Rivalier (1929) wrote It may well be that trichophytin—analogous in this respect to tuberculin—beha es as pseu antigen capable of being used for the detection f a pre xisting stat of sensi tisation but incapable of ind cing similar state However like tuberculin trichophytin is able to bring about desensitisation and as such deserves to rank in the therapeutic arsenal against dermatophyte

disease and in this respect we incline toward the views of a number of workers. No precise technique for its use appears to have been devised. A general direction is to inject intradermally [illegible] c.c. of trichophytin repeating this dose once a week or as soon as the first reaction has disappeared. The dose should be increased so soon as the first one loses it effect. These are merely suggestion.

9. *Sensitization by Dermatophytes to Substances other than Trichophytin.* The trichophytin reaction has already been described as a group reaction with the implication that, with a few rare exceptions, it may be positive for diseases produced by all the dermatophytes. Notwithstanding that very rarely it may be found to be positive in other mycoses, caution is necessary in attributing such reactions to non-dermatophyte infection for apparently healthy individuals are able to exhibit positive reaction.

The production of antibiotic substance like penicillin (Peck and Hewitt 194[illegible]) explains certain reactions observed in individuals sensitized by dermatophytes after penicillin injections. Peck (19[illegible]0) distinguished amongst the reactions produced by penicillin (*a*) the urticarian and erythematous type caused by penicillin itself and appearing after a period of 5 days to 1 week; (*b*) the spontaneous type caused by sensitization by dermatophytes; this reaction of a trichophytid type appears after 48 hours. For completeness it is necessary to include reactions caused by products accompanying penicillin such as retarding substance.

Thus via parasensitizations the dermatophytes are [illegible] issuing from the restricted field of the dermatophyte infection to a much larger field including the various trichophytids where puzzling pathological reactions are frequently to be found.

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CHAPTER IX

Haplomycosis

EMMONS (1948) gave the name haplomycosis to a fungal disease of rodent caused by *Haplosporangium parvum* Emmons and Ashburn 194 . This organism was isolated *from the lungs of 6* per cent *of the* pock t mice (*Perognathus*) examined by Emmon and Ashburn (194) whilst investigating the incidence of *Coccidioid mmiti* amongst the rodent in the region of San Carlos Arizona. Other rodents were found to be naturally infected (e g *Dipodomys Citellu* etc) In Canada Dowding (194) found 14 infected animal out of 271 rodent taken in Alberta. Characteristic spherules were encountered in the lung. Thirteen of the infected animal were *Peromyscus* (*Peromyscu maniculatu boreal* white footed deer mice) and one was a red squirrel (*Sciuru hudsonicu bu leyi*). Of these 14 cases, *Haplosporangium parvum* was isolated from 6. Whereas in Arizona the greatest dimension of fungal cell obtained w 45 μ in *Alberta spherules as large a 270 μ with wall thickne 8 t 10 μ* were seen

Th lesions in rodent haplomycosi are discret and confined to the lung tissues. They usually form a poorly developed granuloma. Analogous lesions were experimentally reproduced by intranasal inoculation int white mice by Ashburn and Emmons (1945). The experimental lesion however exhibited a tendency towards spontaneous regression aft r 4 t month. Ashburn and Emmons nevertheless consider them to be mor than a mere tissue reaction in respon e to the presence f foreign bo lies. They support their view as follows (i) by th fact that killed spor do not produce this reaction by the appearance of a perivascular lymphocytic infiltration at a distance from the granulomatou focu ( ) by the k but regular growth of the le ions for 4 or month

Within the tissues of naturally infected rodent the p thog n appears rounded cell which attain a diameter of 10 to 14 μ As noted these dimension may be very much great r Endo p rulation characteristic of *Coccidioid mmit* ha ne er been ob erved Th protopla m dense non vacuol ted nd basoph lic In the la experimentally infected mice the fung l stru ture ttam d meter f 40 μ after two month These spherules re n k ped by a thick mem brane having several layers th y includ a larg entral sph ie m d n 5 to μ wide containing a basophil c nu le du 1 0 t w in 1 met r There no endosporulation *In short the spherical tissu f rm of Haplosporang um parv m* resemble young spherules of *Cocci* ...

On an acid dextrose agar *H parvum* grows more slowly than *C immitis* and at first appears as a glabrous and colourless disc The centre and then the periphery rather rapidly becomes downy The down which is at first white browns with age Numerous individual variations may be found from strain to strain certain colonies remaining wholly or partly glabrous

The but slightly segmented mycelium is rather well branched The branches arise at random from the main hypha without any reference to septation The hyphae are at least 1 µ in diameter and occasionally may attain 4 µ

The spores are somewhat rounded 3 to 3 5 µ in diameter with an apiculate membrane though older spores may have a completely smooth wall They are borne singly or in short chains of two or three at the end of hyphae or upon more or less branched lateral sporophores Emmons and Ashburn (194) regard these spores as monosporous sporangia or sporangiola which they call conidia These conidia are attached to hyphae or conidiophores by a delicate filament from which they are separated at maturity by a septum

Dowding has obtained laboratory cultures on soil agar from Canadian strains and has evidence that the sporangia are not readily detachable from their sporophores but are very adherent She considers rodents to be infected when they dig their burrows

Haplosporangium parvum belongs to the genus *Haplosporangium* Thaxter 1914 containing three known species namely *H bisporale* Thaxter *H decipiens* Thaxter both isolated from horse dung and *H lignicola* Martin 1937 isolated from rotten wood *H parvum* is differentiated from these three species by its much smaller spores

Dowding (1947) believes that *Blastomyces dermatitidis* and *Histoplasma capsulatum* may have affinities with *Haplosporangium parvum* *Coccidioides immitis* might have had less obvious connections with these except for the fact that Emmons considers it to be a Phycomycete with monosporous sporangia though he has obtained from cultures sporangia enclosing two or three spores

Emmons and Ashburn (194) prepared a substance called haplosporandin which produced a positive reaction in 20 out of 33 individuals who reacted positively to coccidioidin

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CHAPTEI X

The Histoplasmoses

It is possible to distinguish human histoplasmosis or Darling disease epizootic lymphangitis of the Equidae and perhaps histoplasmosis of rodents. The first of these will be dealt with more fully than the other two which will be only outlined.

A HISTOPLASMOSIS IN MAN

Definition

Histoplasmosis is a mycosis of the reticulo endothelial system caused by *Histoplasma capsulatum* Darling 1906. It is characterized by anaemia leucopenia and hepatosplenomegaly. The denomination of this mycosis has rarely been in question; it is sometimes called Darling's disease.

Historical

Histoplasmosis was first recognized by Darling in 190 whilst seeking cases of kala azar in the region of the Panama isthmus. The organism found in the tissues was regarded as a protozoan and named *Histoplasma capsulatum* by Darling in 1906 when he discovered two new cases. In 1913 da Rocha Lima in a comparative study of sections from histoplasmosis lymphangitis of solipedes and kala azar came to the conclusion that the agent of histoplasmosis was not a protozoan but a fungus. The fourth case of histoplasmosis, the first to be found after Darling's report, was described by Riley and Watson in 1926. It was not until 1934 however that Monbreun confirmed da Rocha Lima's findings by cultivating the pathogen from the blood of a young child whom Dodd and Tomlin (1934) had recognized during his life time to be subject to histoplasmosis. The mycological study of the organism carried out by de Monbreun merely left to his successors the problem of its systematic. De Monbreun contributed a further essential fact by isolating the pathogen from a dog and demonstrating that it may be inoculated into young puppies. This author further proposed that the name Darling's histoplasmosis should be replaced by Darling's cytomycosis. Further contributions to our knowledge of histoplasmosis were made by Van Pernis Denson and Hollinger (1941) and also Zarafonetis and Lindberg (1941) who demonstrated the cutaneous sensitivity to histoplasmin of patients suffering from histoplasmosis; these authors regarded this reaction as specific. The important work of Emmons and his school on the etiology of the disease will be given later.

Importance and Geographical Distribution

Like the other great visceral mycoses histoplasmosis is rare, the literature recording about 100 cases. It attacks without racial distinction individuals of two age groups: early infancy and the fourth, fifth and sixth decades. Whereas children are affected regardless of sex, histoplasmosis in adults affects twice as many men as women. There is a slight preponderance of cases amongst agricultural workers. The youngest case on record is undoubtedly that of Schlumberger and Service (1944) who diagnosed histoplasmosis *pre mortem* (by sternal puncture) and *post mortem* in a male child seven weeks old on entering hospital, who died two weeks later from hepatosplenomegaly and anaemia.

The histoplasmosis cases are mainly found in the states of the Middle West of the U.S.A. (Missouri, Minnesota, Michigan) but it is a disease of world wide distribution. Cases are on record from the following regions: South Africa, South America (Argentina, Columbia, Brazil, Uruguay), England, Austria, Hawaii, Java, Mexico, the Philippines, the Sudan, Venezuela.

Etiology

The etiology of histoplasmosis is not yet known with certainty, but work in progress suggests that it is a disease of rodents which may be transmitted to dogs, cats and man. De Monbreun (1939) first discovered a case of histoplasmosis in the dog; he showed the strain of *Histoplasma capsulatum* isolated to be identical in all respects with those isolated from man, and that it could be inoculated by mouth to young dogs. In 194[illegible] Emmons, Bell and Olson published an account of their work in Virginia. They captured 1,6[illegible]0 rodents in the Loundoun County region where four cases of human and three of canine histoplasmosis had been recorded and demonstrated the presence of *Histoplasma capsulatum* in one mouse and ten rats. Large anatomo-pathological lesions were not found in the animals from which the fungus was isolated and the parasite was mainly isolated from the liver and the spleen.

The method used by Emmons and his co-workers in making these isolations consisted of performing an autopsy with sterilized instruments upon newly killed animals, the abdomen having first been covered with a solution of cresol. Fragments of viscera (spleen, liver, suprarenals, lungs, bladder, kidneys) were then cultured on Sabouraud's medium whilst other fragments of the same viscera were preserved in formalin until after [illegible] to 4 weeks' incubation at 30 C the result of the culture was positive or negative.

Olson, Bell and Emmons showed at about the same time (1947) that they could obtain cultures of *Histoplasma capsulatum* from crushed ticks (*Dermacentor variabilis*) previously fed on a dog naturally infected with histoplasmosis. However, four dogs placed in contact with the first one showed no disease symptoms.

In 1940 Emmons, doubtless inspired by his success in his study of

coccidioidomycosis isolated two strains of *H capsulatum* from 387 specimens of earth taken from a farm where he had captured 7 rats infected with histoplasmosis Further he demonstrated the presence of macro conidia or echinulate chl mydospores characteristic of *Histoplasma capsulat m* in aqueous suspensions of the two specimens which yielded these strains Thus it is e ident th t this parasit find in soil a medium f ourable t it reproduction in the saprophytic stat

Pathogenic Agent

The binomial *Histoplasma capsulatum* wa proposed by Darling in 1906 when the organism was known only in its parasitic form and was moreo er regarded a protozoan I spit of this confu ion at the beginning there i no good reason for not retaining Darling s name for the agent of hist plasmosis De Monbreun lso took this view when as the first to olate the parasit he furnished a complet description of it

How er the following synonyms are encountered in the literature—

Cryptococcus capsul t Castellani and Chalmers 1913	*Torulopsis capsulat* (Darling) Moore 1934
T rulopsis capsulat Almeid 1933	*Sepedon um* sp H smann and Schenck en 1934
Posadasia pyriformis Moore 1934	*Histoplasma pyriforme* (Moore) Dodg 193

Stained by Wright or Giemsa *Histoplasma capsulat m* ppears in the blood marrow or the iscera a round or oval body with a greatest width of 1 to 4 μ I most cases it is an intracellular inclusion within the cells of the ret culo ndothelial system in macrophages and giant cells It is en loped by a refringent capsule of ariable thickness which does not stain by the usual procedures One end of the cell is often less thick than the other budding occurs t this acuminate extremity It is the occurrence in the widest region of a crescent shaped mass of chromatin that supports a resemblance between *H capsulatum* and a *Le shmania* Howe er the absence of blepharoplast distinguishes it from a Leishman Donovan body

The isolation by Monbreun f the parasit in pure culture from the blood of child infected with histoplasmosis demonstrated the dimorphism of the organism which ha a yeast like aspect in the parasitic condition but is filamentous in culture It is in fact possible to obtain both phases in culture the yeast lik phase called YP by American workers has the same morphology as that of the organism in the tissues whil t the mycelial phase (MP) ha the aspect of filamentous fungus

There is no outstandingly characteristic feature t distinguish colonies of *Histoplasma capsulatum* The yeast like phase ppears as small brilliant whitish colonies whilst the mycelial phase appears as whit down which assumes a brownish colour after two weeks

The colonies of the mycelial phase are made up of segmented branched

hyphae 2 5 µ wide Besides the ordinary chlamydospores often in chains they also give rise to large round cells 20 µ in diameter by the expansion of terminal or lateral filaments These cells contain numerous fat globules Their wall thickens and develops excrescences very irregular in form and length which may reach to 6 µ These rounded cells with rough and uneven walls form the dominant feature of the mycelial phase of *H capsulatum* they are called echinulate chlamydospores stalagmospora (Ciferri and Redaelli) and macroconidia (Emmons) The echinulat chlamydospores arise both on aerial and vegetative mycelia In fact various types have been described According to Howell (1939) sporula tion of the mycelium gives rise to (i) spherical or pyriform tuberculate

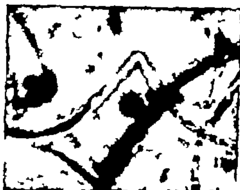


Fig 40

Histopl sma cap lat E hinulat l lam do pore on l our l medium t ordinary temperature (× 1000) (R produced from Furl *H stopl smo is in Brazil* th thor permission

spores 10 to µ in diameter either sessile or borne upon short pedicel of the aerial mycelium (ii) round or oval spore 5 to 30 µ upon short pedicels of the submerged mycelium and (iii) round or oval spore sessile or borne upon short pedicels of the aerial or submerged mycelium Howell and others consider that the two last spore types re only transi tional pha es in the formation of the tuberculat spores which are the *mature forms* Whilst recognizing that the structure of the hinulat chlamydospores do not permit of their being regarded a d Monbreun calls them ascus like bodi or ascus like cells Moore appears to have been the only one t regard them asci

The mycelial phase always appears in the absence of any part cular precautions and the y ast like phase lways tend to pro r ss t ard it Howe r slightly acid pH (6) slightly levated t mperature ( ) and abundant aeration are fa ourable factors The mycelial phase al y appears on Sabouraud s med um on dextrose gar potato g latin or on bread whatever the incubation temperature

De Monbreun drew att ntion t the need for using hydrochloric and not acetic acid t adjust the pH of the culture medium In fact acetic acid a well as small amount of sodium cetate prevent the development of the fungus

Colonies of the yeast lik phase are made up of void cells 3 to 4 5 μ long which bud only t their acuminat end the buds remaining attached for some time to the mother cell by a thin filament often as much as μ long In stained preparations the chromatin is in the form of a crescent near the rounded end of the cell There is thus no essential difference in the appearance of *H caps lat* m in the tis ue and in culture f the y t like phase

It is just a difficult t get and keep the yeast like phase a it is ea y to bt in the mycelial phase There appear to be four necessary conditions ( ) a temperature of t least 37 C for below that temperature the cultures revert inevitably t the myc lial phase (ii) a medium rich in protein preferably containing rabbit blood or that of another animal human blood being excellent (iii) a high degree of humidity drying ausing reversion t the mycelial phase and ( ) a fa tor the nature of which is not yet fully det rmined but which probably inv l es the level of CO_2 concentration in the atmosphere surrounding the culture It has hitherto been correctly thought necessary t seal the culture tubes hermetically to obtain the yeast like phase of *H cap latum* This doubtless not only ensures the maintenance of a certain degree of humidity but also establishes a sufficiently high concentration of CO in the cultures factor of even greater importance Indeed according to B llen the yeast like phase of *H capsulatum* a well as that of *H farcim nos m* may be obtained by culturing in an atmosphere containing 1 to 20 per cent CO The CO may not be replaced by nitrogen and a low ring of the percentage of CO_2 to below 15 per cent causes reversion t the mycelial phase

In ord to obtain the yeast lik phase other less obvious conditions are necessary In particular it is essential to culture on solid media Salvin (1947) was unable t obtain the yeast like phase on liquid media such a broth serum or broth conta ning 1 per cent serum H obtained it however on a semi liquid medium with the following composition—

Proteose peptone Dif	10 g
Neo peptone Dif	3 25 g
Tryptose	3 2 g
Glucose	g
Sodium chloride	5 g
Disodi m hydro n pho phat	0 g
Agar	1 5 g
Distilled water q	1 000 ml

On this medium the optim m pH f r growth l tw 6 l and 8 l The temperature of 37 C is ess tial f r at 2 or 31 the re is a reversion to the mycelial phase Optimum vi sity is btained w th 1 75 g of agar

in 1 000 ml but the agar may be replaced by a silicon salt According to Salvin perfect development is obtained under anaerobic conditions in mixtures of 10 20 40 and 80 per cent of CO_2 with air and least in 100 per cent oxygen Salvin claims that this medium is better for retaining the yeast like phase than one containing blood

Further all workers agree that the yeast like phase can only be maintained by frequent transfer every 3 to 5 days

As has been seen the addition of blood to the medium is not absolutely necessary The yeast like phase can be obtained on a serum medium or on Petragnani s medium without malachite green

The transition from the yeast like to the mycelial phase has been observed by de Monbreun by transferring a culture of the yeast like phase to an agar plate (Sabouraud s medium) at laboratory temperature The yeast like forms enlarge and round up until they reach 4 to 5 times their original diameter these cells give rise to a mycelial filament which segments and yield secondary filaments

A number of workers have been interested in obtaining the yeast like phase from the mycelial phase with rather contradictory result Only Ciferri and Redaelli (1934) and Conant (1941) appear to have succeeded in culturing *H capsulatum* at 37 C on a blood medium in sealed tubes According to Campbell (1947) it is quite easy to recover the yeast like phase by transferring every 2 to 3 days from the mycelial form kept at 37 C to the following medium which is a modification of Francis s medium (cf sporotrichosis)—

Veal broth	1 000 ml
Rabbit or horse blood	80 ml
Peptone	10 g
Glucose	10 g
Sodium chloride	g
Cystine or cystine hydrochloride	1 g
Agar	20 g

The agar salt and peptone are added to the broth which is heated until the agar dissolves The cystine is dissolved in sufficient caustic soda solution to adjust the pH to 6.0 to 6.8 then added to the mixture This is sterilized at 120 C for twenty minutes and after cooling to 60 C the blood and glucose are added under sterile conditions Shake repeatedly for 3 hours at 60 C and tube out

It is certain however that when only the mycelial phase is available the easiest way to recover the yeast like phase is to inoculate into an experimental animal and to recommence isolation of the yeast like phase from the diseased organ

Symptomatology

It is difficult to give a precise picture of all the symptoms of histoplasmosis but in some it is worth recalling its similarity to kala azar

g anaemia leucopenia splenomegaly emaciation and prolonged fever The disease persists from some three weeks to 8 months and in exceptional cases for 4 8 10 and ev n 16 years

In a child the most important signs are temperature digesti troubles and diarrhoea followed by obvious hypertrophy of the spleen and liver and also of the lymph nodes Death follow a state of advanced cachexia

In adults the dis often t kes a slower course nd extensive invol e ment of certain organs may giv a strong bia and render diagnosis difficult According to Miller *et al* (1947) 50 per cent of the cases show le ions of the skin nd of the m cous membrane According to these workers the cut neo mucous manifestations may be grouped in 5 categories—

1 Ulceration and granulomatous tumours f the buccal mucosa (28 of 4 patient xhibiting cutaneo m cous lesions)
 I apules patches cutaneon ulceration (11 out of 4 patient)
3 Purpuric lesions capable of ulceration (patient)
4 Abscesses furunculoid lesions (rare)
5 Localized or generalized dermites (rare)

Pulmonary manifest tions re frequently noted a well as gastro intestinal troubl such a diarrhoea miting haemorrhage perforation According t Parsons and Zarafonetis (194) lesions of the middle ear were found in 8 cases and in one of Crumaine cases the parasit was found in the pus from an otitis media

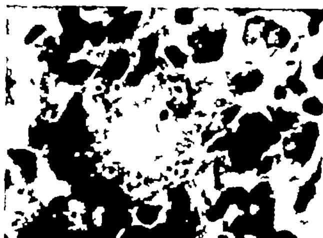
Other d eases able t reach the reticulo endothelial ystem may be found associated with histoplasmosis This is particularly true for tuberculosis (5 cases) and Hodgkin disease (cases) Confusion w th the latter is possible even from the hist logical standpoint and several authors (Miller *et al*) insist upon the presence of cells strongly reminiscent f Sternberg Reed cells in tissues ttacked by histoplasmosis

Two good fundamental works n the symptomatology of histopla mosis are those of Parsons and Zarafoneti (194) and of I ark (1948)

Histopathology

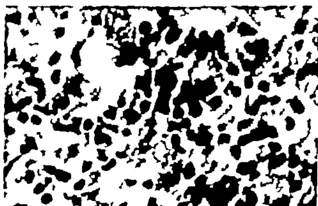
Histoplasma capsulat is a sentially an intracellular parasit found mainly within the cells f the reticulo endothelial system Its presence conditions the formation of granulomatous processes ending with necrosis ulceration or calcification The parasit is found most readily in the li er spleen lung lymph nodes and bone marrow Duart (194) demonstrated it in the central nervous ystem and the meninges he considers that if the parasite has not been more often described in the encephalon and it annexes t is because it ha not been systematically looked for

Destruction of hepatic cells with centro lobular necrosis has been observed in the li er the sinuses are filled with tightly packed macro phages as well as Kupffer cells of the parasites



F[illegible] 41

Histoplasm[illegible] [illegible] ... cell[illegible] [illegible] [illegible] ... of *H*[illegible] ... (R[illegible]produced from [illegible] ... [illegible] with [illegible] permission.)



F[illegible] 4[illegible]

H[illegible] ... (R[illegible]produced fr[illegible] ... [illegible] ... permission.)

In the lung there is massive infiltration by large mononucytes and the alveoli are collapsed

It will be noted in general that the tissues are invaded by large mononuclear elements and that there is no polynuclear infiltration

Treatment

There is no effective therapy in histoplasmosis. However a few cases of recovery have been reported when sulphadiazine was used. It is interesting to note that Campbell and Saslaw (1951) demonstrated the ineffectiveness of streptomycin injection in mice infected experimentally with *H capsulatum* and this antibiotic had a stimulating action upon the mycelial phase *in vitro*. On the other hand the same authors showed that actidione affords partial protection to mice against *H capsulatum*

Prognosis

The fatal prognosis in children must not be applied without reserve to adults. It seems that in certain cases the disease may become limited after a process of fibrosis. Some cases of recovery have been claimed but in practice these are better disregarded

Differential Diagnosis

Tuberculosis, leukemia, kala-azar and Hodgkin's disease should be differentiated from histoplasmosis. There is a report of a wrong diagnosis of amoebiasis in a case in which intestinal troubles were predominant. There may be possible confusion with Hodgkin's disease on account of the presence of elements resembling Sternberg Reed cells in the tissue. Park (1946) reported the formation in the liver of accumulations of parasites strangely similar to the pseudo cysts produced by toxoplasm. Quite clearly no clinical argument is able to replace the demonstration of the parasite in smear preparations or sections or its isolation through culture

Laboratory Examination

The blood exhibits moderate anaemia of the hypochromic type with red blood count of 3 to 4 million or even less. Leucopenia is frequent but not general and sometimes associated with a relative lymphocytosis

The blood proteins show an alteration in the albumin globulin ratio with relative increase of the latter

Albuminuria is frequent. The urine may yield red and white cells and the organism has been cultured from urine

Mycological Diagnosis

Mycological diagnosis involves searching for the pathogen and isolating it in culture

1 Search for the organism in the blood is rarely successful for the histoplasms are confined to the monocytes. It is more profitable to search

marrow obtained by sternal puncture. The same also applies to smear preparations made from sections of portions removed by biopsy. Staining of blood or marrow smears is carried out with Wright or Giemsa.

The demonstration of *H. capsulatum* in sections is effected by the usual basic stains, namely eosin haematoxylin, Masson's trichrome, Van Gieson, Goodpasture, Gram Weigert and Giemsa. The capsule may be stained by Heidenhain and most silver impregnation methods.

For distinguishing histoplasma from leishmania, Pará recommends the *use of Gram's method as modified by Krajian (1949) or else Foshay's method (1931).* With Krajian the histoplasma are violet or greenish blue whereas the leishmania are pink red. With Foshay the histoplasma are stained blue and the leishmanias mauve. It is noteworthy that the parasitic form is Gram positive and slightly acid fast.

Isolation of the parasite by culture is undoubtedly the best method for diagnosing histoplasmosis. Parsons and Zarafonetis (194) indicated *that in 23 instances where the pathogen was cultured positive cultures* were in 18 obtained from tissues, in 9 from blood and in one from marrow. *It appears that where a search for the pathogen in blood smears is usually* negative, it can be isolated often enough by blood culture.

Inoculation is carried out on Sabouraud's medium at ° C or at 37° C on blood medium in sealed tubes. The culture tubes must be retained for four weeks on account of the slow development of the parasite.

In a case of generalized histoplasmosis Dublin, Culbertson and Friedman (1948) were twice able to culture the pathogen by removing 5 ml of blood in a syringe containing 1 ml of sodium citrate. The mixture was kept at laboratory temperature and two weeks after removal of the blood mycelium appeared above the layer of white globule.

Experimental Inoculation

*It is too frequently ignored that Darling un*successfully attempted animal inoculation of histoplasmosis. Having failed to culture the organism he was limited to using infected human tissue as his source of material for inoculating guinea pigs. De Monbreun was more fortunate, having at his disposal cultures of *Histoplasma capsulatum*. From the yeast like phase and by means of intravenous injection he produced in two monkeys (*Macaca rhesus*) lesions similar to those found in man and also macrocytic anaemia, lymph node hypertrophy and hepatosplenomegaly. Death occurred 14 days after inoculation and the pathogen was recovered from the monocytes of the circulating blood during the life time of the animal but from the tissue after death. Failure attended the use of the mycelial phase *to inocul te a monkey*.

Inoculation of an animal with a culture from the mycelial or the yeast like phase permits the recovery of the pathogen from various organs after several months. Except in certain cases, however, the lesions do not become generalized as in man and in most cases the animal recovers. According to Emmons, Bell and Olson (194) mice and guinea pigs do

not exhibit any further symptoms after the acute phase of the infection but it is possible two years after the inoculation to isolate the pathogen from the liver and spleen The dog which is one of the animals spontaneously infected can easily be infected in the laboratory even through the digestive tract (De Monbreun) However the lesions do not become generalized Brandt (1950) showed that it is possible to induce a generalized effect if the inoculation is preceded by X irradiation of the animal

Catanei (194) working with an African strain observed no generalization in the mouse and the guinea pig but he was able to isolate the pathogen from the spleen two months after inoculation

Allen (1948) inoculated histoplasmosis into mice and guinea pigs via the nostril and the ear and the result was positive in 70 per cent of the mice and 75 per cent of the guinea pigs respectively He concluded that in nature infection occurs via these two routes

The varying results obtained by different workers tend to support the view that there are considerable differences in the virulence of the different strains of *H capsulatum*

Histoplasmin

First prepared in 1941 by Van Pernis Benson and Hollinger histoplasmin is a metabolic product of *H capsulatum* developed in the culture medium Its intradermal injection produces reactions similar to those of tuberculin It soon became apparent that histoplasmin inoculation not only gives a positive reaction in those attacked by histoplasmosis but also in apparently healthy individuals Two sets of fact have emerged from the very numerous epidemiological studies that have attempted to clarify the real significance of this reaction—

1 The extent to which the histoplasmin reaction is positive varies according to the geographical origin of the individuals tested Thus Reimann and Price (1949) showed that whilst 78 per cent of the resident of Missouri gave a positive reaction the corresponding figures for Pennsylvania and Northern California were 9 to 11 per cent and only 3 per cent respectively Those regions which yield the greatest number of reactors are also the ones which have the largest number of cases of histoplasmosis

2 The percentage of positive reactions varies with the presence of pulmonary calcification in the individuals tested In studying the value of the test with nurses Palmer (194) showed that whereas per cent of them as a whole reacted to histoplasmin the proportion was 85 per cent in those who had pulmonary calcification Similarly from Tennessee residents Christie (1950) obtained 87 per cent of positive reactions in those with calcifications whilst in those without calcification the percentage was half as great Further only 18 8 per cent of those with calcification reacted to tuberculin and the whole population gave only 18 6 per cent of reactors positive to tuberculin

Olson Bell and Emmon (194) were however unable to establish a clear relationship between the presence of pulmonary calcification and the extent to which there is positive reaction to tuberculin or histoplasmin

In any case conclusions drawn from many epidemiological investigations at present support the view that histoplasmosis exists in a mild form very much more widespread than the serious form recognized up to the present and that this mild form is in certain regions responsible for a great many cases of pulmonary calcification previously attributed to tuberculosis Nevertheless the use of histoplasmin does not permit of diagnosis of histoplasmosis and there are still cross reactions between histoplasmin and blastomycetin

Prior Cole and Torbet (1949) claim however that this test has a specific value in the case of the dog

Histoplasmosis in Africa

As yet little attention has been paid to this question even though it possesses an interest out of proportion to the number of the cases reported namely cases 1943 and 1946 (Duncan) 1 case in 1947 (Friess and Delvoye) and other cases (Kerman and Arctas) This interest stems from two facts—

1 The lesions noted are mainly cold abscesses some of which tend to heal

2 The parasite recovered from the lesion has greater dimension than those usually given (10 μ in diameter instead of 3 to μ) and it is usually extracellular

It is not unreasonable to speculate as to whether this is a distinct species Catanei (194) who made an exhaustive investigation of one of these African strains makes no special comment upon this apart from it poorly marked pathogenicity

Taxonomy

Moore (1934) erected the genus *Posadasia* after having considered the echinulate chlamydospores to be asci However de Monbreun who first described them regarded them as no more than ascus like bodies or ascus like cells and it is generally agreed that they are not asci

In 1934 Ciferri and Redaelli proposed the family Histoplasmaceae and reconsidered this question with Vivocchi in 1938 These authors believed that the Histoplasmaceae should be placed near the Nectaromycetaceae Ciferri and Redaelli 1929 and the Torulopsidaceae Ciferri and Redaelli 1929 within the larger family of the Adelosaccharomycetaceae (Guilliermond) *sensu ampliore* Ciferri 1940 The Histoplasmaceae comprise the single genus *Histoplasma* Darling 1906 of which there are three species *H capsulatum* Darling 1906 *H farciminosum* Rivolta and Micellone 1883 and *H muris* (Shortt) Ciferri and Redaelli 1934 The conception of Ciferri et al is based essentially upon the yeast like aspect of

H capsulatum in its parasitic phase whereas when cultured the fungus has both a filamentous and a yeast like phase In spite of objections Ciferri and Redaelli (1948) have maintained their point of view

Hansmann and Schenken (1934) having assigned a fungus isolated from a case of histoplasmosis to the genus *Sepedonium* Howell (1939 1940 1941) compared the morphology and physiology of *Histoplasma capsulatum* with various species of *Sepedonium* (*S chrysospermum* and *S xylogenum*) with *Stephanoma tetracoccum* with *Chlamydomyces palmarum* and with *Mycogone perniciosa* *Sepedonium chrysospermum* forms aleuriospores identical with the echinulate chlamydospores of *H capsulatum* and also phialospores *Sepedonium xylogenum* does not form phialospores and its aleuriospores although similar in morphology to the echinulate chlamydospores of *H capsulatum* are of different origin *Stephanoma tetracoccum* forms phialospores and its aleuriospores are different from the chlamydospores of *H capsulatum* *Chlamydomyces palmarum* and *Mycogone perniciosa* form aleuriospores and phialospores which seem to justify the assignment of these two species to the genus *Sepedonium* Howell concluded that the genus *Histoplasma* constitutes among the *Fungi imperfecti* a distinct genus possessing certain morphological affinities with the genera which he has studied

From the facts here put forward it appears that the family Histoplasmaceae may be retained for the genus *Histoplasma* but it is absurd to assign this family to the Adelomecetchromycetaceae which are yeasts for the Histoplasmaceae are filamentous fungi with a yeast like form

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B EPIZOOTIC LYMPHANGITIS IN SOLIPEDES

Epizootic lymphangitis in solipedes is a transmissible contagious and spontaneously curable disease caused by *Histoplasma farciminosum* (Rivolta and Micellone 1883) Ciferri and Redaelli 1934. In the horse the ass and the donkey it produces nodular lesions often ulcerated which spread along the lymphatics and reach the ocular nasal and buccal mucosa. The disease was originally centred on North Africa especially Algeria but from there many cases have reached a world wide dissemination since the First World War (1914–18).

The pathogen often referred to as *Cryptococcus farciminosus* (or *farciminosus*) was long thought to be a protozoan. In 1912 Da Rocha Lima assigned it nearer to *Histoplasma capsulatum* suggesting at the same time the fungal nature of the two organisms. Attempts at culture have been made since 189 by Marcone 1896 by T... 1898 by Baruchello and 1906 with a certain amount of success by San Felice but Negre and Boquet in 1918 obtained the first series of cultures and transmitted epizootic lymphangitis of the horse by their use. Some years later Bardelli (1924 1925 1926) in turn isolated the cryptococcus inoculated his culture in the horse and even prepared a vaccine. Nègre and Boquet and also Bardelli were able to culture the filamentous form of the pathogen by inoculating pus into a fairly simple medium such as Sabouraud with the addition of crushed lymph node (Negre and Boquet) or thymus (Bardelli) from the horse. Upon these media the yeast like forms characteristic of the pathogen in the tissues enlarge and then give rise to mycelial filaments which yield chlamydospores and what Nègre and Boquet called external spores. The latter which are undoubtedly

CHAPTER XI

The Levuroses

Introduction

The levuroses are diseases caused by true yeasts. There are two types of such diseases, namely moniliasis caused by *Candida albicans* and torulosis or cryptococcosis caused by *Torulopsis neoformans*. As will be seen later there are certain other species of *Candida* besides *Candida albicans* which possess some pathogenicity but in practice only *Candida albicans* and *Torulopsis neoformans* are of importance in this respect.

A precise definition of a yeast is not easy to give, though it is generally accepted that the yeasts are fungi which reproduce only by budding. But the ability of certain filamentous fungi, e.g. *Histoplasma, Sporotrichum, Blastomyces* to reproduce by budding under certain conditions either in the saprophytic or the parasitic state renders this definition void. According to Skinner in Henrici's work "The yeasts are true fungi of which the habitual and dominant developmental form is unicellular". Skinner thus clearly emphasizes the dominant morphology and not budding. On the other hand the ability of many yeasts to form a pseudomycelium brings them nearer to the filamentous fungi, even though the budding mode of formation of the pseudomycelial filaments distinguishes them from the characteristic germination of true mycelial filaments. Lindegren (194) showed the budding process involves the extension of a tube from the central vacuole to a region of the cell wall which becomes thinner as it forms an excrescence upon the mother cell. Within this excrescence which later becomes the daughter cell the vacuolar tube penetrates and sets up the vacuole of the daughter cell. The two cells separate by a basal constriction at the identical position where the excrescence was formed. When having reached the size of the mother cell the daughter cell separates from it a new yeast cell arises capable of producing similar buds which either separate or remain attached. If the daughter cell continues growth in one direction to form a filament which in turn may bud off others a pseudomycelium results. The pseudomycelium made up of filaments and rounded elements ... is a complicated branched system the morphology of which was recognised as sufficient basis by Langeron and Talice (1932) for the separation of generic distinctions. Langeron and Guerra (1938-40) gave the name blastesis (*blastese*) to a pseudogerminative process described in 1930 by Roux and Linossier. In cultures of *Candida* there is the appearance

creation of the genus *Candida*[1] whilst Stelling Dekker's work (1931) on the sporogenous yeasts and the papers of Lodder (1934) and of Diddens and Lodder (194) on the asporogenous yeasts are noteworthy. Lodder and de Minjer (1947) have classified the asporogenous yeasts into two families the Rhodotorulaceae and the Torulopsidaceae. The Rhodotorulaceae are asporogenous yeasts which develop a red pigment of a carotinoid nature. These yeasts have neither pathogenic nor fermentative power. Very widespread in nature, they are frequent contaminants of culture media inoculated with pathological product. The Torulopsidaceae are asporogenous yeasts placed into two sub-families according to whether they form a pseudo mycelium (Mycotoruloideae) or not (Torulopsoideae). The latter comprise six genera *Torulopsis*, *Pityrosporum*, *Mycoderma*, *Kloeckera*, *Trigonopsis* and *Schizoblastosporion*. Only the genus *Torulopsis* characterized by the formation of a thick capsule includes a pathogenic species, namely *Torulopsis neoformans*, the agent of torulosis or cryptococcosis. The Mycotoruloideae comprise three genera *Candida*, *Trichosporon* and *Brettanomyces*. According to Langeron the genus *Trichosporon* which forms a true mycelium ought not to be classed with the yeasts; it includes the species *T. beigeli*, the agent of the white piedra. The *Trichosporon* species are in any case distinct from those of *Candida* and *Brettanomyces* for they form arthrospores. The *Brettanomyces* species (cf Custers 1940) are Mycotoruloideae distinguished by the ogival form of their cells and intense acidification of the culture medium under aerobic conditions. They are of practical interest only to the fermentation industry (*Brettanomyces bruxellensis*, *B. lambicus*). The *Candida* species are Mycotoruloideae with the yeast form rounded or oval and the pseudo-mycelium forming a complicated structure ornamented with elaborate whorls. Some *Candida* species are pathogenic, the most important of these being *Candida albicans*. Diddens and Lodder have distinguished species of which 13 are saprophytes and [illegible] are pathogenic. The *Candida* species are distinguished from one another by their fermentation action on sugars and the nature of their sugar or nitrogen assimilation. Only the *albicans* group (*C. albicans*, *C. triadis*, *C. stellatoidea*, *C. truncatus*) form chlamydospores. These characters distinguish them sharply from other Mycotoruloidea.

Skinner (194) recognizes three families of imperfect yeasts:

1. The Sporobolomycetaceae which St lling Dekker [illegible] and basidiomycetes but which Skinner considers to be imperfect fungi probably related to the basidiomycetes.

2. The Rhodotorulaceae corresponding to the Rhodotorulaceae of Lodder.

[1] Th [illegible] Faculty of Medicine [illegible] of Lam [illegible] of [illegible] of V [illegible] lation [illegible] Institute [illegible] Faculty of Medicine [illegible] Institute [illegible] of Tropical Medicine [illegible] University of Exeter, England.

3 The Cryptococcaceae corresponding to the Toruloptsd ease of Diddens and Lodder The Cryptococcaceae are divided into two sub families the Cryptococcoideae (Toruloptsoideae of Diddens and Lodder) and the Candidoideae (Mycotoruloideae f Diddens nd Lodder) The Candidoideae re distributed mongst three genera Form which prod ce blastospore only are put in the genus *Candida* or the genu *Brettanomyces* those which produce botl blastospore and arthrospores are put in the genus *Trichosporon* tho which prod ce arthrospores but no bl stospores are excluded from the family They include such organ ms as *Geotrichum candid m (Oid m lact)*

In the case of imperfect yeast the spec es is based eventually on such biochemical haracters a can be d duced from f rmentation studies and the ssimilation of sugars or of nitrogenou substances Lan ron and Guerra reserv the name fermentation for the anaerobic breakdown f sugars accompanied by the formation f carbonic cid The term sugar selectivity refers to the capacity of a y st to met bolize this or that pure sugar The English terms are ga production (C) and acid production (A) The ssimilation of nitrogenous substa ces emphasizes the capacity of yeast to utilize one or another nitrogen compound generally an amino cid a their sole nitrogen source

The stability of the f rmentation characters of y st ha been m ch discussed Most thorities regard them st bl en when transition occurs from phas R t phase S According t Langeron and Guerra who are amongst the most rdent supporters of this iew apparent divergencies of result are due to three main causes—

1 The use of yeast strains contaminated by bacteria These bact rial inf ctions may persi t for long time

The use of mixed strains It often happens that a number f yeast strains the colonies from which represent mixture rathe than single strain are isolated from pathological prod ct F rment tion studie from these gi aberrant result unless the m xture should in olv zymatic and azymatic yeasts

3 The u of impure sugars

According t Kluyver (1930 1938) there are tw principal types of enzyme constitution enzyme formed by micro organi ms irrespecti of substrat and adaptation enzymes which result from chemical stimulation The capacity to form adaptation enzymes is transmitted from strain to strain but may disappear if the composition of the culture medium is altered According t Rhoade (1941) m tation could bring bout stable modifications in the formation of enzymes From th it would seem that there are tw causes f ari tion in fermentation capacity e adaptation and mutation

Rhoades carried out his experiments with *Saccharomyces* In medical mycology as hitherto practised the stability of enzymes may be accepted for the determination of *Candida* species provided that the cond tions a

indicated above namely purity of the strains and purity of the sugars are scrupulously respected. George and Plunkett (1948) investigating ten strains of *Candida albicans* kept for 3 to 4 years in the laboratory noted morphological modifications in six of them but not one showed the slightest alteration in the fermentation characters.

A THE MONILIASES

Definition

The name moniliasis is given to acute, sub-acute or chronic infections caused by yeasts belonging to the genus *Candida* and chiefly to the species *Candida albicans*. The skin and the mucosa are most frequently involved.

The term moniliasis is used in current publications and should be retained. As Skinner has noted (194) it would be regrettable if modifications in the systematics of the genus in question should once more determine a change in the nomenclature. The older nomenclature is of two kinds: either it is derived from the taxonomic names of the causal agent and one thus refers to oidiosis, torulosis, cryptococcosis, mycotorulosis, saccharomycosis; or it involves dermatological terms of a primarily topographical nature e.g. thrush, perlèche, onychia, paronychia, vulvovaginitis. These terms are usually corrected by the addition of the name of the pathogen responsible ... *M. nilia albicans* ...

Historical

In 1839 Langenbeck recognized the presence of fungi in thrush. Almost simultaneously Gruby (184) who had studied this disease for more than a year called the fungus of thrush aphtophyte. Robin (1853) named the pathogen *Oidium albicans*. The term *Oidium* was unfortunate enough for it is applied to the imperfect form of Erysiphaceae (ascomycetes pyrenomycetes) and cannot be retained. It may be thought apposite to recall here that Pasteur's first paper on alcoholic fermentation which formed the basis for all subsequent studies on fermentation was published in 18 . In 1868 Quinquaud first changed the name *Oidium albicans* to *Syringospora robinii*. Quinquaud having recognized the non-validity of the name *Oidium* several workers consider the generic name *Syringospora* to have priority over that of *Candida* which was accepted in 1939 by the Third International Congress of Microbiology. In 188 Plaut named the pathogen *Monilia candida* and in 1890 Zopf ... *Monilia albica*. This last appellation prevailed in the literature up to the work of Berkhout in 1923. *Monilia* cannot however be accepted for it is applied to the imperfect form of *Sclerotinia* (ascomycetes discomycetes) the agent of brown rot in fruit.

Since the beginning of this century interest in moniliasis has received a strong stimulus from the work of Castellani (cf. Castellani 19) ... not only described bronchomoniliasis but he was the first to ... the

Accord... Langenbeck ... first ... phenomena ... fungus

pathogenic yeasts on a fermentation basis In 1923 Berkhout theirs created the genus *Candida* which has since been retained and separated it from many other fungi of similar morphology

In 1928 Ravaut and Rabeau in an eminent work established the levurids and drew attention to a product of this group which they called le urin

In 1931 Benham through original work and an important critical review of the literature showed that a classification based on purely morphological or purely biological considerations was insufficient to distinguish the *Monilia* from one another and that most of the strains isolated from pathological materials belonged to the species *C albicans* Langeron and Talice in 1932 tried to distinguish between morphological groups within the genus *Candida* but in 1938 Langeron and Guerra denounced this basis of separation as inaccurate and produced their work on the fermentation reaction of the yeasts of the genus *Candida*

The work of Lodder (1934) and of Diddens and Lodder (194) exerted great influence upon the classification of the anascosporous yeast

Importance and Geographical Distribution

Moniliasis is a relatively frequent mycosis of world wide distribution Though it is found at all ages in both sexes and without racial distinction certain predisposing factors are recognized Malnutrition favours moniliasis of the mucous membranes obesity that of the folds and diabetes and pregnancy probably encourage the development of vulvo vaginitis caused by *Candida albicans* Therapeutic baths damp dressings frequent immersion of the hands in water and the handling of fruit are frequently thought to favour the disease Five cases of endocarditis were reported in drug addicts who regularly subjected themselves to subcutaneous injections the role of the injection or of the drug is unknown

Etiology

Candida albicans is normally present in man Its incidence increases in the intestine with age and may increase considerably in certain pathological or therapeutical conditions Administration of antibiotics in particular seems to increase the number of yeasts in the excrement at the same time diminishing that of bacteria

Todd (1937) whilst searching for *C albicans* in the mouth and the throat found it in 42 per cent of 50 persons more than 50 years old in 7 2 per cent of 284 young students and in 20 per cent of 72 adult women Out of 614 young people he isolated it in 8 7 per cent of 498 males and in 17 7 per cent of 316 females Of 1 000 persons under observation 140 yielded *C albicans* and 7 gave non determined yeasts 9 3 per cent of these were males and 18 per cent females In addition this same worker noted agglutination of *C albicans* by the serum of 22 5 per cent of 1 150 normal persons 30 4 per cent for women and 15 7 per cent for men

Castellani observed a certain incidence of bronchomoniliasis amongst tea tasters in Ceylon Törnell (1946) blamed the dust from corn threshing

for certain pulmonary alterations attributed to yeast. Nilsby and Norden (1949) tried to demonstrate the presence of *C. albicans* in the atmosphere. 600 petri dishes exposed to the air in a town did not give a single colony of the organism in question. The same result was noted for 110 exposures in houses or hospitals. However, petri dishes placed on bedside tables of patients with *C. albicans* in their buccal cavity have yielded some colonies of the fungus. Nilsby and Norden have also searched unsuccessfully for the organism in dust from threshing and reject Tornell's hypothesis. In the buccal cavity of healthy men they have found *C. albicans* in 30 per cent of their cases and in 6. per cent of patients with pulmonary disease. Their conclusion is that *C. albicans* is rarely found outside the human body.

Skinner (1947) however had already emphasized the rarity of the strains isolated outside the human body, and he noted from the collection examined by Diddens and Lodder that only two strains came from soil. According to Skinner it is a mistake to regard *C. albicans* as widely spread in nature. One would expect the organism to be prevalent on dairy produce and he has on several occasions isolated it from Camembert cheese. Again he has drawn attention to the work of Mrak, Phaff and Vaughn (194) who isolated it from dates and of Mrak and McClung (1940) who isolated it from grapes.

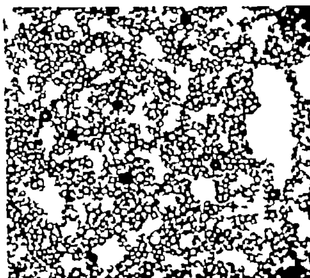
Candida albicans is thus a yeast which is frequently isolated from man, healthy or otherwise, and also from dairy produce and fruit. It is apparently more frequent in women than in men and it is more frequently isolated from patients with lung trouble than from healthy individuals. It is probably a saprophyte of widespread distribution which under particular conditions can become pathogenic.

Pathogenic Agent

The *Candida* species are yeasts which grow easily at laboratory temperature upon numerous media and especially upon Sabouraud per cent glucose medium. Inoculation at a point on agar and white con... moist creamy growth that appears within 48 hours which ... filament rather quickly into the depth of the agar. If inoculation is carried out in streaks instead of at a point and especially if the medium is penetrat... into the agar filament appear on either side of the streak in ... The aspect of *Candida* colonies varies with the type of inoculation ... *inoculation yields a more or less circular colony which ... at the height of its growth. We define as adult colony ... Langeron and Guerra ... one which has ... used to grow the ... on ... the quantity of medium offered to it and the surface ... To obtain the adult colony it is sufficient to ... and petri dishes and Erlenmeyer flasks are unnecessary.

Importance has been attributed to the characteristics of the ... on liquid as well as solid media. When ... broth it usually produces ... turbidity and ... the

bottom of the tul Y t des lej in the form of lej out and their growth often k es the liquid me l m clear they also often prod ce a consi tent ring t the gl /air int rfa t wh h import nc ha l n att ched If the rin d v lop t wards the centre it ntually forms a v il which is described a m com if it de cends t the bott m f the tube in small fragment and membranous if it fall witl d fficulty and i l rger portions A v l only x ptionally see young cultures f *Candida C trop l* how f rm a mucous l t w rd the fifth day



I 43
C l l B Chlam d pore l rth C mea

A fragment of a cre my colony mounted in l n l sodine show a larg number of round elliptic cells 2 t 4 / in size many f wh h are bout to bud If the colony sli htly kl or if a fra ment of agar conta ning filaments is carefully pre ed bet een l lide and slip w thout t ang it out the mode f filament formation h cteristi of *C ndida* species an be seen The arion specie cannot h w be distin uished on the basis f the arious morphologies re nized by Langeron and Talice

The most important morpholog cal haract is undoubtedly the formation of chlamydospores by th *Cand la* specie f the *lbicans* group (*lbica* *C trop* (*stellatoi l* ((*ncata* The chlamydospores are larg spherical cells to 8 / or m re diameter refringent double contoured and wh h sually arise t the nd of the fil ment Acidophil and acid f st the no bud unless the medi m is hanged According to Kligman (1950) thre ondit on fa our the

development (i) a poor culture medium (ii) reduced oxygen pressure and (iii) a low temperature Culturing at 37 C clearly inhibit the formation of chlamydospore Long ago Benham demonstrated the value of using agar with maize flour for their production

Though they can arise upon undifferentiated hyphae the chlamydospores usually form upon a swollen articulation of the mycelium which was termed a protochlamydospore by Langeron and Guerra (1938) The protochlamydospore is full of very condensed protoplasm is acid fast and can itself change into a chlamydospore or empty its contents into another chlamydospore which may arise from it Protochlamydospores most frequently yield single terminal chlamydospores but bunches of three or four or short chain may develop from them

It has long been observed that the macroscopic morphology of yeast colonies varies with transplantation Colonies which are creamy at their first isolation often become membranous after a more or less lengthy period By analogy with bacteria the expression phase S is given to the creamy phase and phase R to the membranous phase These dissociation or variation phenomena in *Candida* colonies have given rise to a great deal of research since the time of Fermier s original observations in 1890 Phase S differs from Phase R in the following respects—

1 There is predominance of the yeast phase over the mycelial phase Whereas the creamy colonies practically only contain yeast cells about the bud the membranous ones chiefly consist of pseudo mycelium with elements of greater dimension than those of the creamy phase

In liquid media phase R always forms a veil whilst phase S forms at most a ring and exceptionally a mucous veil

3 The transition from phase S to phase R reduces and can the disappearance of the pathogenicity

Yet other forms have been distinguished such as form L (lethal form) (MacKinnon 1940) which tends to disappear if it is not frequently transplanted Langeron and Guerra (1941) have correlated with these phase variation the appearance of dark and clear sectors in certain yeast colonies notably of the genus *Candida* the clear sectors contain small rounded cells and the dark ones very large cells

It has been observed that in an abundant culture medium which is well aerated and rich in assimilable carbohydrate the S form predominates and tends to maintain it If Phase R appears with diminishing oxygen if the culture medium is poor (maize agar gelatin carrot or potato) or if the culture is set up in a liquid medium giving partial anaerobiosis Acidity favours phase S and alkalinity phase R

It is important to note that the transformations are not irreversible and that it is possible to pass easily from phase R to phase S and that whatever morphological modifications appear in the yeast the fermentation properties remain unaltered

The genus Candida has numerous synonyms of which the following are the most important —

Sporotrichum aneum Cruby 184; *Oidium* Link 1809 and Robin 1853; *Syringospora* Quinquaud 1868; *Monilia* *aneum* Plaut 1885 non *sensu* Bonorde; *Cryptococcus* Kutzing 1833 Vuillemin 1901; *Zymonema* de Beurmann and Gougerot 1909; *Mycotorula* Will 1916; *Monilia* Gmel 1791 Vuillemin 1911; *Blastodendrion* Ota 1924; *Mycetoblastanon* Ota 1924; *Mycotoruloides* Langeron and Talice 1932; *Mycocandida* Langeron and Talice 1932; *Geotrichoides* Langeron and Talice 1932

The most important species from the pathogenic point of view is *C. albicans* (Robin 1853) Berkhout 1923. According to Conant *et al* (1947) this species has 172 synonyms, a few of which are—

Oidium albicans Robin 1853; *Syringospora robinii* Quinquaud 1868; *Monilia candida* Plaut 1885 non Bonorden; *Monilia albicans* Zopf 1890; *Endomyces albicans* Vuillemin 1898; *Monilia pinoyi* Castellani and Chalmers 1913; *Monilia psilosis* Ashford 1917; *Mycotorula albicans* Langeron and Talice 1932

The identification of the various *Candida* species rests essentially upon study of the fermentation power, sugar selectivity and nitrogen assimilation. For the *albicans* group one must add the presence of chlamydospores. The tables given by Langeron and Guerra (1938) are reproduced with slight modification.

FERMENTATION OF SUGAR

(Zymogramme in peptone water with the addition of sugar)

Group	Species	Glucose	Levulose	[illegible]rose	Maltose	Lactose	Raffinose	Le[illegible]
ALB[illegible]	albicans, triadis, [illegible], tropicalis							
Trop[illegible]	tropicalis, [illegible], pelliculosa							
P[illegible]	pseudotropicalis							
[illegible]	guilliermondii, [illegible]							+
Krusei	krusei, parakrusei, [illegible]							±
Brumpti	brumpti, [illegible]	±						
Asteroides	[illegible]							

SUGAR [illegible]

Group	Species	Glucose	Sucrose	Maltose	Lactose	R[illegible]
ALBICA[illegible]	albicans	+	+	+	−	
	triadis	+	+		−	
	stellatoidea	+		+	−	
	truncata	+	+	−	−	
TROPICALIS	[illegible]	+	+	+	−	
	[illegible]	+	+	+		
	[illegible]	+	+	+	−	
PSEUDO TROPICALIS	pseudo tropicalis	+	+	−	+	
GUILLIER MONDI	guilliermondii	+	+		−	
	[illegible]	+	+	+	−	
KRUSEI	krusei	+	−	−	−	
	parakrusei		+	+	−	
	[illegible]	+	+	+	−	
BRUMPTI	brumptii		−		−	
	flareri	+	+	+		
[illegible]	[illegible]	+	−	−	−	
	[illegible]			−	−	
	[illegible]	+	+	+	+	

NITROGEN ASSIMILATI[illegible]

Group	Species	Peptone	Asparagin	[illegible]	[illegible]	[illegible]
ALBICA[illegible]	albicans triadis stellatoidea truncata					
TROPICALIS	[illegible]					
PSEUDO TROPICALIS	pseudo tropicalis					
[illegible]	[illegible]					
KRUSEI	krusei parakrusei [illegible]					
BRUMPTI	brumptii flareri					
[illegible]	[illegible]					

The present t nd ncy is to con id r th groups a sp ies and species a arieties.

B sid the biochemical characteristics indicated abo the *Cand* species ha e certain morphological charact rs of value in their identifi tion. *C. albicans* ar *stellatoidea* forms star shaped colon s n blood a (Jones and Martin 1938). *C. albica* ar *truncat* (Vanbr[illegible] 19

produces filament which run over the surface of the agar nd the adult colony has truncated pex *C albicn* var *triad* prod es a mucous veil in liquid medi *C krusei* forms a thick eil in liquid medi Biological characters may also be considered in conjunction with these *C tropicalis* and *C albicans* are the only *Candida* pathogenic for the rabbit *C albicans* (and its group) *C tropical* *C krusei* and *C guilliermondi* are probably the only ones pathogenic for man and *C albicans* is by far the most frequently encountered

Symptomatology

The moniliases are localized or generalized muco cutaneous nfections and much more rarely in olve the v cera

A Muco-cutaneous Moniliases

1 Cutaneous Lesions The most frequent form is intertrig The lesion takes the form of a reddish patch following vesicle formation Frequently there is running sore and fissure dev lopment t the bottom of a fold F ut and Rabeau (1938) consider that the contour of the patch is characteristic it is finely notched irregul r shredded edged with a thin epidermal ridge whitish detached to the extent of about 1 mm The lesion smarts or itches violently When situated in an inguinal fold it rarely in ades the scrotum and the penis but frequently the intergluteal region In women t ften spread to the labia majora

Other frequent localizations are the infra mammary f lds the axillae the umbilicus and the interdigital folds of the fingers and toes In the hands in 50 per cent of the cases the lesions are lim ted to the third inter digital space and are ne er found in the first space

From the interdigital spaces of the feet the lesions may travel up the back of the foot forming circinated erythematous and esculous patches

2 Onychia paronychia *C albicans* frequently i ades the periungual fold Amongst American workmen handling fruit the disease may be regarded almost ocational The skin above the ungual fold becomes red stretched tumefied and painf l and slight pressure may cause the exudation of drop of pus Onychia is commonly described if the lesions were due to the presence of *C albicans* i *sit* but uthors are usually discreet about the exact de scription of the lesions Lewis and Hopper (1948) neatly discriminat between the onych f moniliasis and that caused by dermatophytes It is t once apparent they writ that the cardinal signs of tinea unguium namely crumbling yellow colour and loss of lustre together with lack of paronychia readily distinguish the tw conditions Pa aut and I abeau (1938) however claim that the nail becomes opaque and thickened raised by a hyperkeratotic mass and that it i often impossible t differentiate it from a nail attacked by a trichophyton

W believ that the onychia associated with *C albicans* is the result of trophic troubles caused by the paronychia The nail does not ppear

to be invaded by the yeast Vanbreu e ghem (19 0) has in any case shown that *in vitro C albicans* is incapable of attacking keratin [1]

3 Muco-cutaneous Lesions Perleche which invades the commissure of the mouth and may spread to the cutaneous lining may be regarded as a muco cutaneous form The whitish blotches which cover the red margins of the lips become progressively erythemato squamous

Becau e of the frequency of cutaneous involvement vulvovaginitis may equally be considered in this group Frequent in pregnant or diab tic women it is characterized by copious white emission vulvar pruritis and often by erythemato squamous le ion of th outer vulva and the inner surface of the thighs

4 Mucous Lesions Vulvovaginitis uncomplicated by cutaneous lesions comes together with thrush into this group Thru h is a stom titis which may or may not leave the tongue intact characterized by a white lustreless coating which adhere to the mucous membrane It is found *especially in individual suffering from malnutrition*

5 Generalized Lesions Spread of a moniliasis to the muco cutaneous lining is exceptional When it appears all th symptoms already giv n in a more or less mixed form may be det ct d Scalp involvement with folliculitis decalvan appears to be frequent in these case (cf Cra Lambelin and Vanbreu ghem 19 0)

Two form may be distinguished one of earliest infancy and that of later infancy The latter which i rarer i al o more re istant to treat ment The first form may p s into the econd In adult generalized monili ses of the skin hav been reported following prolong d therapeutic baths and moniliase have been extended by the use of damp dressing

B Visceral Moniliases

The best known i bronchomoniliasis the first information having been provided by Castellani in 1 10 It is however ry much less frequent than thi worker at first thought to be the case Diagn is m t be given with extreme caution The sputum mucoid nd g l tinou is usually colourless sometimes tr aked with blood th cough i refractory

Pulmonary monilia is ha also been described of varied rad log l report and a a generally gra condition M ny of the e de ribed how ver are r lly secondary inf ctions f ld tuberculur ... ronchial dilations and cancerous lung

Five ca es of ndocarditis h been reported in drug addict who injected them l es d ily In four of the cases *C parapsi* w sol ted and in the fifth *C guilliermondi*

C Granulomas caused by *Candida albicans*

Moore (1948) nd Hauser and R thman (19 0) ... gran lom roduced by *C albicans* In Moore ... there wa a lesion in the back

Th ... w ... hat ... t ... w ... l at normal ... remain unaltere l

of the hand 9 cm by 7 5 cm w th a rai ed margin and a granulated centre Histopatholo ical e amination re ealed rare yeast forms in the tissues Hauser and Rothman in addition t their a tual case report 13 cases in the literature The c es are certainly very rare

Histopathology

When there are granulomatous le ions yeast cells filament gi nt cell and epithelioid cells are found in the ti ues



F 44
T tm t potas um iod i of i u pected of l ng bron l om l

Treatment

Cutaneous and m cous moniliases may usually be treated fairly easily One f the most ffecti treatments for cutaneous monili ses is to apply a 2 pe cent alcoholic solution of eosin Whitfield ointment and Castellani paint may also be used (cf Dermatophytoses) Onychia and paronychia are treated by bathing with 1/4 000 potassium permanganate or applying in the form of wet dressings f llowed by 1 per cent gentian violet

Vulv aginitis yields easily t borate or bicarbonate injections Where diabetes is present this naturally has also to be regulated

Thrush and Perleche re et fa ourably t application of 10 per cent glycerinic borat The general state of the patient has often to be impro ed as it is often an important factor in the progression of the disease

The broncho and pulmonary moniliases re treated with potassium

(*g*) *Biochemical properties* Having obtained a pure culture from an anascosporous yeast which forms filament the shape of which is round it is permissible to conclude if it forms chlamydospores that a strain of *Candida albicans* has been isolated In the absence of chlamydospores one cannot be certain that one is not dealing with *C albicans* because certain strains do not infallibly produce them For identification of the species fermentation and sugar selectivity as well as the assimilation of nitrogenous materials must be studied

Note The very great frequency with which *C albicans* may be isolated from the human body especially from sputum indicates the need for the greatest caution in interpreting a relationship of cause and effect



Fig 4

Cutaneous test with oidiomycin or monilin ... ted f ... b ... ng bronchomoniliasis

between the isolated yeast and the disease in question When bronchomoniliasis or pulmonary moniliasis is suspected the diagnosis is only justified if *having eliminated all other possibilities C albicans* (or *C tropical*) is isolated frequently and abundantly from sputum Only then may potassium iodide treatment be resorted to

4 Experimental Inoculation

The rabbit is the best animal for studies of the pathogenicity of the *Candida* species A 1 ml intravenous injection of a slightly opaque emulsion of *C albicans* kills the rabbit in 4 or 5 days Lesions in various viscera mainly the kidneys and brain are readily found

A subcutaneous injection may cause an abscess in 48 hours

To a less extent *C tropicalis* is pathogenic for the rabbit The other species are not

Allergy and the Levurids

Antibodies (precipitins agglutinins) are readily demonstrated in the serum of healthy individuals or patients these reactions have only group specificity and are inconclusive from a diagnostic point of view According to Todd (1937) the agglutinin titre does not usually go beyond 1 160 but Conant *et al* claim a much higher titre of 1 400

Ravaut and Rabeau (1928) showed that there could appear generally on the occasion of growths rising at the level of initial lesions and mainly at the time of relapse or following a levurin injection lesions which they called levurids These almost invariably symmetrical lesions develop on the arms forearms axles buttock the inner surfaces of the thighs the face and may be localized or generalized They comprise salmon pink brick red maculous efflorescences at a level at which the skin is more or less infiltrated they are rarely pruriginous (Ravaut and Rabeau 1936)

The levurid have the general characters of id (cf dermatophyte infections) they are sterile and heal by treatment of the initial focus

Ravaut and Rabeau prepared a substance which they called levurin (monilin oidiomycin) by a method similar to that used for trichophytin Injected intradermally into patients with moniliasis it may produce—

1 A local reaction similar to that which follows trichophytin injection i e immediate reaction of the urticarian type late reaction of the tuberculinic type

2 A focal reaction in the form of an eczematiform growth at the margin of parasitic constituent

3 A local reaction on a site previously injected with levurin

On the other hand a reaction which has died down can be resuscitated by a revival of the parasitic focus

The intradermal reaction to levurin has no specific value it is a group reaction Its absence from a moniliasis patient would be abnormal but cases of anergy are recognized Its presence in a healthy subject does not justify any conclusion

There are no cross reactions with trichophytin sporotrichin or tuberculin

Moniliases in Animals

Rapidly reviewing the literature while dealing with mycotorulaceous parasites in hedgehog, Talice (1932) drew attention to cases of thrush in the hen (Neuman) the lamb (Delafond) the cat the dog the turkey (Blanchard) in *Cercopithecus patas* var *ruber* (Thiry 1913) and in the calf and the foal (Brumpt) Catanei (1925) noted Monilia on the tongue of the

Algerian monkeys (*Macacus innus*) without pathological symptoms. Talice reported that of 8 hedgehogs 6 yielded Mycotorulese, 5 of which were *Mycotorula (Candida) albicans*, the yeast being isolated from the intestine. Careful autopsy revealed no lesion.

Hart (1047) observed in recent years in Australia an epidemic of moniliasis in turkeys and hens caused by *C albicans*. Of 00 to 900 turkeys 350 of them 5 to 8 weeks old 300 died, only birds of this age group were infected. Autopsy revealed lesions in the crop and a thick exudate on the mucosa with a tendency towards the formation of false membranes. Hart was able to arrest an epidemic by replacing the drinking water with a 1 – 000 solution of copper sulphate, a method previously recommended by Hinshaw in 1933.

Taxonomy

The *Candida* species are anascosporous yeasts which probably represent imperfect forms of ascosporous yeasts with ascomycetous affinities. The introduction to this chapter discusses this viewpoint in greater detail.

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B TORULOSIS OR CRYPTOCOCCOSIS

Definition

This disease which has several synonyms such as *Torula* meningitis yeast meningitis Busse Buschke's disease European blastomycosis is a chronic one with the essential symptomatology of an af[illegible] meningitis accompanied by violent headache and considerable hypertension of the spinal fluid

Historical

The [illegible] agent was first isolated by Bu[illegible] in 1894 from a subperiostal lesion of the tibia of a w[illegible] man The pathogen was in 1910 called *Saccharomyces hominis* by Vuillemin

In 1894 however Sanfelice isolated the same organism from fruit juice in Italy and called it *Saccharomyces neoformans* thus *neoformans* must be retained whatever the genus to which the organism concerned in torulosis should be assigned

In 1916 Stoddard and Cutler first isolated the pathogen from the brain and marrow of a man They called it *Torula histolytica* for they believed that they had an instance of tissue destruction caused by a yeast capsule

Redaelli in 1931 assigned the pathogen to the genus *Torul[illegible]* when according to the work of Lodder it should apparently remain The name

[illegible]

of the organism should thus be *Torulopsis neoformans* (Sanfelice 1894) Redaelli 1931

Todd and Herrmann (1936) described the formation of a monosporous ascus and called the yeast *Debaryomyces hominis*

In 1937 Redaelli, Ciferri and Cavedano claimed to have confirmed the observations of Todd and Herrmann but regarded the epithet given by their compatriot Sanfelice as preferable so that according to them the agent of torulosis was *Debaryomyces neoformans*

Most of those who have dealt with torulosis have however been unable to confirm the observations of Todd and Herrmann and of Redaelli *et al* It is thus pertinent to inquire whether there are several agents of torulosis or only one agent able to reproduce by means of ascospores under circumstances as yet undefined

In Western Europe the first case was described in Holland by Steeners (1934) the second was apparently the Belgian case of Bussche, Scherer and Thomas (1938) though these workers did not isolate the pathogen and their diagnosis is purely histopathological the third was the French case of Germain and Morvan (1938) followed eight years later by a fourth (or second French case) of Debré, Lamy, Nick, Crumbach and Normand (1946)

Importance and Geographical Distribution

Torulosis is a cosmopolitan disease of which there have been about 1[illegible]0 cases described up to the present Though the infection was first described in Europe only 3 French 1 Dutch and 1 Belgian case have as yet been recognized Most of the instances have emanated from the United States and Australia takes an important place with some thirty cases

No race is particularly prone to torulosis and no predilection for any particular profession has been noted Most cases have been found between the ages of [illegible]0 and 60 with men twice as frequently attacked as women

Etiology

Torulopsis neoformans occurs naturally as a saprophyte and indeed Sanfelice in 1894 isolated it from fruit juice It has since been found in wasps nest on grass the bodies of insects butter and turned milk The strains isolated from sources such as these are not always pathogenic however Rabinowitch experimenting with 40 strains under laboratory conditions found only 8 to be pathogenic though *Torulopsis* isolated as a pathogen from human sources always proved to be pathogenic for mice

The method by which this yeast gains access to man is obviously important It is frequently held to be via the respiratory tract but usually on inadequate evidence Wade and Stevenson (1941) attempted intranasal instillation in mice and were able to produce some rhinitis and in one case pulmonary lesions but no cerebral lesion Yeast cells were however retrieved from the top of the nasal cavity upon the septum and

the turbinate bone (*cornet*) and in the sinuses In several cases lesions occurred as far as the cribriform plate but in no case was the brain affected The mucous membrane of the nose eroded and formed large cystic masses but prior to the appearance of this erosion the infiltration of yeast cells could be found for a long distance below an apparently intact mucous membrane

Debre Lamy Leblois Nick Crumbach and Normand (104) claimed that in their case the penetration was via the skin In fact in their patient a small cutaneous tumour situated upon the chin and rich in yeasts appeared whilst his symptomatology was that of Hodgkin's disease and shortly before his death from a *T neoformans* meningitis

Experimentally as will be seen all routes of inoculation may terminate in the production of cerebral lesions for the brain and especially the meninges are the essential regions of attraction for these yeasts

Pathogenic Agent

The view of most of the classical and modern workers is that *Torulopsis neoformans* is a non filamentous yeast which does not form asco pores It reproduces by buds which have the special features of being mostly single and of having a very narrow neck The cells are perfectly spherical and surrounded by a thick mucilaginous capsule the thickness varying with the strain the age and the culture medium The cell diameter is 4 to 6 μ that of the capsule 1 to 2 μ in culture

In tissue the cell vary considerably in form and diameter some cells are to 3 μ and others 10 to 15 μ They are usually round but some of them are ovoid whilst others as Wade and Stevenson (1011) have expressed it resemble a deflated rubber ball half of which has sunken into the other

Even when cultured on agar slides no filamentation appears

Torulopsis neoformans is easily cultured on all the usual media and a very abundant growth can be obtained on glucose agar within 48 hours at laboratory temperature On this medium the colonies are moist shining viscid whitish at first then slightly brownish On a blood medium they have a dry appearance They grow well on Raulin where they develop flakes at the bottom of the tube In per cent glucose broth they develop feebly at the bottom of the tube without disturbing the medium In a medium which has ethyl alcohol as the only source of carbohydrate they develop moderately

Torulopsis neoformans does not ferment sugars but it seems able to use several of them in acidifying the medium glucose malt sucrose but not galactose or lactose

By Beijerinck's auxanographic method it can be seen that it utilizes glucose fructose mannose galactose sucrose malt se lactose ammonium sulphate asparagine urea peptone but not potassium nitrate

Todd and Herrmann (1196) first described a sexual cycle for *Torulopsis neoformans* and this was confirmed by Fedsalli Ciferri and Giordano

(1937) According to these workers *T neoformans* on a maltose or glucose Sabouraud medium reproduces by budding for five or six weeks but as soon as the medium dries up two types of cell appear having thin and thick walls respectively Both of these cell types can bud but if they are transferred to van Tieghem cells in broth the thin walled cells put out a tube towards those with thick walls The latter produce only slight protrusions which join the tubes from the thin walled cells the contents of which empty completely into the thick walled cells

After this fusion the central mass which Todd and Herrmann call the spheroid surround it lf with two membranes the outer one of which is undoubtedly the thick wall of the mother cell The spheroid is then ejected int the medium and begins to bud

Todd and Herrmann reserve the name *Cryptococcus hominis* for the non sexual phase and call the sexual phase f the pathogen *Debaryomyces hominis* Redaelli Ciferri nd Giordano pply the generic name *Debaryomyces* but the specific name *neoformans* so that in their view the organism becomes *Debaryomyces neoformans*

Lodder and de Minjer (1947) noted that if these f ct are confirmed a mode of ascospore formation is inv lved which is completely different from that encountered in the other ascosporous yeast

A number of research workers ha e directed their attention to the nature of the capsule of *Torulopsis neoformans* Kligman (1947) showed that the capsule is essentially compo ed of polysaccharides but he was unable to produce in the rabbit either agglutinins precipitins or anti bodies producing complement fixation either by injecting the whole cell the cell deprived of it capsule or the capsule alone Th essential features of Kligman s technique for obtaining the capsular substance are as follows

An emulsion in distilled water from a two week ld culture grown on potato agar with dextrose is centrifuged and run into 500 ml flasks The centrifugation is repeated four times taking up the residue each time with distilled w ter The last residue is heated for 25 minutes at 5 C in 0 N hydrochloric cid This kills the yeast cells and dislodges their capsule The same result can be btained by warming the emulsion for 12 hours at 56 C The decapsulated cells are removed on the centrifuge and the supernatant liquid neutralized with soda This is followed by the addition of 10 per cent by weight of sodium cetate and 3 olumes of ethyl alcohol which produces an bundant white precipitat After refrigeration overnight the solution is centrifuged and the residue taken up in distilled water an opalescent solution is formed which is precipitated by 3 olumes of ethyl alcohol and 10 per cent sodium acetate After three reprecipi tations a protein free solution is obtained The burette Millon and trichloracetic acid reactions are negative Lugol iodine reaction con firms the absence of starch F hling and Benedict s test the absence of reducing substances Molisch reaction is on the other hand strongly positi e

Drouhet and Segretain (1950) claimed that it is possible to dissolve the *capsules* of *T neoformans* by submitting these yeast to the action of hyaluronidase

Symptomatology

Torulosis is essentially an afebrile meningiti of a chronic evolution characterized by violent and persistent headache The *clinical* symptomatology depends upon the localization of the lesions *and their* importance Generally the symptom develop progre ively and commence with intermittent frontal headache but the onset *may be* fulminating as in the case of Debre *et al* (1946 1947) where there wa a sudden stroke followed by death 15 days later Amongst the *symptom* noted are dizziness stiffness of the neck hemiplegia paraplegia and frequently deteriorating eyesight This is either mechanical or visual ptosi nystagmus strabi mus papillary stasis and papilloedema Vomiting is often noted Troubled sleep and mental disturbance are frequent Depression di orientation apathy agitation irritability and delirium have been noted

In about half the cases the symptom are localized in the meninges and the encephalon In a third of the ca es however there are pulmonary complication and there are some ca e of pulmonary torul is from the start These lesions are vague and indefinite and never permit of a specific diagnosis The symptoms are those of a sub f brile inf ction of sl development sputum i rare or absent sometime blood streaked The pulmonary lesions are usually diffuse and bilat ral but are sometime localized at one side in an upper lobe In the Netherlands ca e of Steenrs (1934) the pulmonary l sion complicating in any case a torula mening tis was fistulized

Besides the le ions of the nervous syst m and f the lung *T neo formans* may occur in th kidney spleen suprarenals liver bronchial lymph nodes sub cutaneous tissue bones and skin The pathogen ha been found in dorso lumbar and inguinal abscesses and in nasopharyng l ulcers

Gill (1934) and Weiss Perry and Shevky (1948) reported tw cases f infection of the orbit leading in the second case to a nu cess r inf tion of both eye

All authoriti insi t in the frequency of the exist nce of t rul si and *Hodgkin* disease or malignant lymphogranulomat sis *which* reckoned at more than 10 per cent What reason are there for the coincidence? The explanations off red may be put int three t gories (i) the coexistence is purely coincidental (ii) involvement of the lymphatic system by *Hodgkin s di ease facilitates inva ion by T neof rmans* This conclu ion was reached by Debre *t al* (1946 194) in the l se f a case in which the lymphogranulomatosis long preceded the appearance f the torulosi which st rted with a cutaneous accident A bi psy which *preceded this accid nt had* hown that the l mph nodes w re indeed affected with Hodgkin disease but free from t rulosis (iii) A third

theory (Kligman and Weidman 1949) would have it that certain cases of Hodgkin's disease may be a consequence of torulosis. By injecting capsular extracts of *T. neoformans* these workers were able to produce a reaction of the lymphatic system which however they did not consider to be characteristic of lymphogranulomatosis.

Histopathology

The whole of the histopathology of torulosis is dominated by the absence of reaction but in the long run the compression effects end by producing chronic inflammatory reactions of a predominantly lymphocytic type. Wherever infiltration has occurred the pathogen is in evidence surrounded by its enormous capsule and imparting a gelatinous consistency to the invaded tissues. The parasite may or may not be surrounded by lymphocytes and giant cells which possibly engulfed it. In meningitic cases the parasite is to be found in the meninges the arteries the perivascular spaces and in the walls of certain arteries outside the internal elastic membrane. The size of the cells is very variable.

Prognosis

In the great majority of cases prognosis is fatal death occurring from 6 to 12 months after the appearance of the first symptom.

Treatment

There appears to be no form of treatment which is effective or which even influences the course of the disease in any way. In fact decompressive lumbar puncture seems to be the only therapeutic method capable of relieving the patient. Shapiro *et al* have performed 133 successive punctures on the same patient.

Nary and Pawson (194) tried out 1 : 10 000 solutions of acriflavine and injected 4. ml of this each day after having removed 60 ml of the spinal fluid without success. Conant *et al* recommend the use of sulphadiazine which must be administered so as to maintain a level of 8 to 12 mg for each 100 ml of blood for several weeks after the disappearance of all symptoms. It is noteworthy however that Jones and Klinek (1945) have found no evidence of inhibition of development in vitro with concentrations of 0 01 0 1 and even 1 per cent sulphadiazine nor even with penicillin (dosage not given). We ourselves have observed a quite normal development of *T. neoformans* upon Sabouraud medium with 2 per cent glucose and containing 500 units of crystallized penicillin per ml.

Potassium iodide gentian violet and thymol have also been used without success. Beck and Voyles (1946) tried the action of potassium iodide and sulphadiazine separately or together upon dogs guinea pigs and rabbits infected with *Torulopsis neoformans*. No therapeutic action could be attributed to these substances.

Kligman and Weidman (1949) investigated the fungistatic activity of

a very large number of products and concluded that not one of them active *in vitro* is active *in vivo*

Differential Diagnosis

Torulosis has been confused with tubercular meningitis cerebral tumour and abscess lethargic encephalitis dementia paralytica and lymphocytic choriomeningitis

Mycological Diagnosis

This involves (i) Search for the presence of yeasts in the tissues pus and spinal fluid (ii) Culture of the pathogen and (iii) Animal inoculation

1 Microscopic Examination

Search for *Torulopsis neoformans* is most ea ily carried out by placin a drop of pus a fragment of cerebral tissue obtained from trep ination or a residue of spinal fluid into a drop of Indian ink Examination is carried out either under a cover lip or after drying the ink film The yeast appear as rounded cells 5 to 1 μ in diameter often in the process of budding surrounded with a capsule which may be enormous and may reach 50 to 60 μ

In the spinal fluid care must be taken not to confu the organism with the blood cells

2 Culture

Typical colonie can be obtained in 4 to 48 hours upon Sabouraud s medium with glucose Animal inoculation of the e cultures permit of reproduction of the human le ion and recovery of the cell with the characteristic large capsules

3 Experimental Inoculation

The most sensitive and frequently u ed animals are the mou rat nd guinea pig The rabbit i not so suitable In the hand of Debre *et al* (1940 1947) the sheep dog monk y (*Macacus*) pigeon and hen remained insensitive

In our opinion the easiest and quick t method for diagnosis is intra cerebral inoculation of the mouse with 0 0 ml of a lightly opalescent emulsion of a culture of *T neoformans* in physiological saline In our experiment this emulsion contained nearly 3 000 yeast cells per cubic millimetre and its opalescence corresponded with th No 1 tube f MacFarland s nephelometer

After having slightly anaesthetized the mouse with eth r th quantity indicated (0 0 ml) i injected with a short needle mounted on a tuberculin syringe into the post rior quadrant of the brain out ide the med n line In most cases the mice tolerat thi proced re well De th o urs in to 8 days In animals which succumb most quickly only cerebral le containing for the most part large numbers of cell surrounded with very

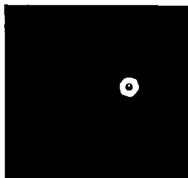
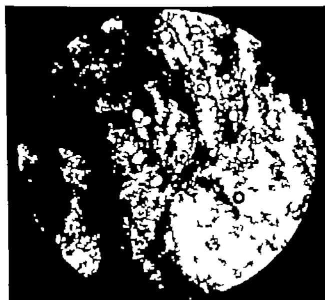


Fig 46

Teri lopa fo me On cell re l ited tl its normous pe l Prepa io in In l an mk fr m fragm nt of mo l



F 4

Teri lopa of ne Ind an mk prepa on from f agm nt of mos l ra

thick capsules will be found In animals dying towards the seventh or eighth days will be found lesions of the lungs liver and spleen A striking feature is the somnolent state of the inoculated animal they would almost be thought dead from the forty eighth hour after inoculation but if they are handled a little it becomes obvious that they retain considerable reserves of vigour Further they emerge spontaneously from their lethargic state to feed

Segretain and Drouhet (1947) carried out subcutaneous intraperitoneal intravenous and intracerebral inoculations of mice and reported that death occurred in 6 to 23 days Intravenous inoculation produced death most rapidly whilst the subcutaneous method was the slowest *These workers considered that the infection always became* generalized and cultures from heart blood were always positive With subcutaneous inoculation a gelatinous mass appeared at the point of injection Peritonitis resulted from intraperitoneal inoculation a covering membrane of *Torulopsis* enveloped the spleen and kidney

Intraperitoneal injection kills the guinea pig in 45 days C neralization *does not occur but there are lesions of the central nervous system* with progressive paralysis of the hind quarters accompanied by tonic clonic contractions before death In the rabbit intravenous injection *does not produce lesions (Segretain and Drouhet 1947 Klagman 194)*

According to Weiss Perry and Shevky (1948) inoculation of a 0 1 ml emulsion of a 4 hour culture with an opacity corresponding to the No 1 tube of the MacFarland nephelometer into the anterior chamber of the rabbit's eye produces a particular kind of lesion Within 5 to days there appears congestion of the sclerotic and lacteal opacification of the cornea The lesion leads to keratitis intra pannus and total blindness (fourteenth to seventeenth day) Rosette shaped images (as the authors call them) appear in the anterior chamber of the eye consisting of a yeast cell surrounded by a simple row of polynuclears and lymphocytes These rosettes are distributed on the anterior surface of the iris and the posterior surface of the cornea This was confirmed by Klagman and Weidman (1949)

The spinal fluid may be clear disturbed greyish or gelatinous it pressure may attain 00 cm of water There is usually but not always an increase in cell number (from 200 to 800) as a general rule lymphocytes predominate The colloidal gold curve is variable but often shows a meningitic or syphilitic reaction The sugar content may be much lowered The Bordet Wassermann reaction is negative

Torulosis in Animals

Frothingham described torulosis in the horse in 190 the lesion was localized in the lung In 1944 Weidman and Ratcliff reported a case in a leopard the first case recognized from 10 000 consecutive autopsies made in the Philadelphia Zoological Garden The first symptom appeared 5½ years after the acquisition of the animal and the illness persisted for

one month The pathogen which was not cultured was found in the spleen kidneys liver the suprarenals lungs and the retroperitoneal nodule

Taxonomy

Torulopsis neoformans is classified in the sub family Torulopsidoideae of the family Torulopsidaceae The Torulopsidoideae which comprise the genera *Torulopsis* *Pityrosporum* *Mycoderma* *Kloeckera* *Trigonopsis* and *Schizoblastosporion* are asporogenous yeasts which do not form a pseudo mycelium whilst the second sub family of the Torulopsidaceae the Mycotoruloideae characteristically form a pseudo mycelium

Torulopsis neoformans is the only member of the Torulopsidoideae in which pathogenic power has been proved Other *Torulopsis* species such as *T rotundata* and *T glabrata* have been suspected of pathogenicity but are probably not pathogenic (Lodder and De Minjer 1947)

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CHAPTER XII

The Mycetomas

Definition

The name mycetoma is given to tumour-like masses produced by various fungi and characterized by the development of tumours, masses and granulations. Actinomycoses caused by *Actinomyces israeli*, already dealt with, once more appears in this category. However, the term mycetoma is usually applied to mycotic tumours appearing in the foot and known as maduromycoses or Madura foot. Many different agents are responsible for mycetomas, and they involve genera far removed from one another. The term mycetoma covers all tumours of fungal origin whatever the systematic position of the organisms concerned: the maduromycoses are mycetomas produced by various fungi apart from those caused by actinomycetes.

Chalmers and Archibald have made a useful distinction between the true mycetomas characterized by the presence of granules and those mycotic tumours devoid of granules which they call para-mycetomas. On the other hand, they call pseudo-mycetomas those tumours having the clinical appearance of mycetomas but which are not caused by fungi.

Historical

H. V. Carter (1860) coined the term "mycetoma" to designate lesions of fungal origin within subcutaneous tissue characterized by tumefaction, fistulization and mycotic granulation in the pus. Brumpt (1905) defined mycetomas as follows: "mycotic tumours formed by felted mycelium and susceptible to external elimination through more or less well developed sinuses". Brumpt also established that these tumours could be caused by very different fungi. Pinoy (1913) proposed a distinction between actinomycoses caused by *Actinomyces* and *Nocardia* species, and the true mycetomas caused by fungi having as their only common characteristic the possession of hyphae wider than those of the Actinomycetes. Chalmers and Archibald (1916–18) put forward the term "Maduromycosis" to denote the true mycetomas. It is thus evident that the term maduromycosis does not embrace all mycetomas. These writers similarly proposed the terms para- and pseudo-mycetoma. Bouffard (1919) distinguished three forms of mycetoma on a clinical basis: suppurating (*suppurée*), sclerotic (*scléreuse*) and cystic (*kystique*). Langeron (1936) classed the mycetomas in two groups: the first includes the actinomycoses or actinomycotic mycetomas, whilst the second contains the maduromycoses

As to the term Madura foot it was according to Carter proposed in 1846 by Colebrook to name foot mycetomas in the region of Madura

Importance and Geographical Distribution

The Madura foot type of mycetoma has a world wide distribution It is however found especially in tropical or sub tropical region

The disease is very much more frequent in male than in female and *particularly in persons of mature age*

Etiology

The mycetoma would appear to be a consequence of wounding followed by subcutaneous inoculation of a saprophytic fungus The disease is met with precisely in individuals who walk bare footed and are exposed to traumatisms The inadequacy of any simple explanation is however pointed out by Langeron (1936) who wrote One may well inquire why *in toto* the mycetomas are accidental diseases and are not much more frequent in view of the multiplicity of opportunities of chance inoculation by fungi Undoubtedly *there is an important factor concerned in the genesis* of this disease which is still completely unknown

Pathogenic Agents

The pathogens of maduromycoses comprise about thirty different species distributed among ten genera The list which follows is probably *incomplete It differs from those found in other works chiefly in two ways* (i) The actinomycetes isolated from cases of maduromycoses seem only to be represented by non sporulating aerobic species which must be assigned to the genus *Nocardia* *Actinomyces israeli* in particular does not appear to have been isolated from Madura foot On the other hand *Nocardia asteroides* seems to be met with only in nocardiosis already defined (ii) The genus *Monosporium* met with in all classifications is suppressed the known species having already been referred by Emmons to *Allescheria boydii* which is the ascocarpic form of *Monosporium apiospermum*

The essential characters of the genera *Madurella* and *Indiella* are briefly given as well as those of *Allescheria boydii* Shear 1922

List of Fungi Isolated from Cases of Maduromycoses

I ACTINOMYCETES

Genus *Nocardia*

1 *Nocardia brasiliensis* (Lindenberg) Castellani and Chalmers 1913

Madura foot species in which the rich chalky (?) and nodular (?) forming colonies adhere to the culture medium The cultures emit an earthy odour The colonies are yellow or orange The granules formed by this *Nocardia* are white or yellowish

Syn *Discomyces brasiliensis* Lindenberg 1909
Nocardia indica Chalmers and Christopherson 1916

Nocardia madurae (Vincent) Blanchard 1896

Non acid fast. Colonies glabrous, humid, soft, wrinkled, cream coloured. Granules white or yellowish.

Syn. *Streptothrix madurae* Vincent 1894
Actinomyces mexicanus Boyd and Crutchfield 1921
Actinomyces mycetomae Greco 1910
Discomyces brasiliensis Pirajá da Silva 1919

3 *Nocardia pelletieri* (Laveran) Pinoy 1913

Non acid fast and with a feeble development of the colonies which are glabrous, acuminate, wrinkled and of mucilaginous consistency. Colour pink to red. The granules are red.

Syn. *Micrococcus pelletieri* Laveran 1906
Nocardia africana Pijper and Pullinger 1927
Nocardia genesii Froes 1930

4 *Nocardia paraguayensis* (Almeida) Conant 1947

Non acid fast species with smooth soft colonies having a whitish centre with the remainder dark in colour. The granules are black.

Syn. *Actinomyces paraguayensis* Almeida 1940

II Ascomycetes

1 Genus *Allescheria*

Allescheria boydii Shear 1922

Starting with granules on Sabouraud grey colonies 6 cm in diameter covered with tufted hyphae of woolly consistency appear in two weeks. The colonies become dryer and greyer upon ageing. The thin walled mycelial hyphae are branched, septate, 1 to 3 μ in diameter and often coremiform. The upright conidiophores terminate with a single oval or pyriform unicellular spore measuring 6.2 to 10.4 μ by 3.7 to 8.7 μ and attached by a flat facet.

Emmons (1944) showed that *Allescheria boydii* is the ascocarpic form of *Monosporium apiospermum* Saccardo 1911.

Ciferri and Redaelli (1950) have established the complicated synonymy of this fungus, which is one of the most frequent causes of maduromycosis in the United States, as follows—

1 *Scedosporium apiospermum* Saccardo 1913
Monosporium sclerotiale Pepere 1914
3 *Monosporium nigricans* Pepere 1914
4 *Monosporium apiospermum* var. *sclerotiale* Pepere 1914
5 *Scedosporium* sp. of Magalhaes 1919
6 *Aleurisma apiospermum* Maire 1921
7 *Cephalosporium boydii* Shear 1922
8 *Dendrostilbella boydii* Shear 1922

9 *Glenospora boydii* Pollacci and Nannizzi 1928
10 *Indiella americana* Delamare and Catti 1929
11 *Scedosporium magalhaesi* Froes 1930
12 *Macrosporium magalhaesi* Dodge 1935
13 *Glenospora viridobrunnea* Redaelli and Ciferri 1934

B Genus *Aspergillus*
1 *Aspergillus bouffardi* Brumpt 1906
2 *Aspergillus chevalieri* Mangin 1909

C Genus *Sterigmatocystis*
Sterigmatocystis nidulans var *Nicollei* Pinoy 1906

D Genus *Penicillium*
Penicillium mycetomagenum Mantelli and Negri 1915

III Fungi Imperfecti

A Genus *Phialophora*
Phialophora jeanselmei (Langeron) Emmons 1945
Syn *Torula jeanselmei* Langeron

B Genus *Madurella*

This genus is represented by imperfect fungi which produce black granules in human tissue and which at 37° C develop upon Sabouraud's medium colonies which remain sterile. The genus *Madurella* erected by Brumpt in 1905 has as type species *Madurella mycetomi* (Laveran 1902) Brumpt 1905. Microscopic examination of the colonies shows them to be made up of wide hyphae (1 to 10 μ) which develop chlamydospores. No other forms of reproduction have as yet been observed.

1 *Madurella mycetomi* (Laveran) Brumpt 1905
Madurella bovoi Brumpt 1910
3 *Madurella tozeuri* (Nicolle and Pinoy) Pinoy 1912
4 *Madurella Oswaldoi* Parreiras Horta 1919
5 *Madurella tabarkae* Blanc and Brun 1919
6 *Madurella ramiroi* Piraja da Silva 1919
7 *Madurella americana* Gammel 1927
8 *Madurella ikedae* Gammel 1927
9 *Madurella rifaanum* Catanzaro 1930
10 *Madurella Lackawanna* Hanan and Zurett 1938

C Genus *Indiella*

The fungi belonging to this group have never been cultured. Their descriptions are thus very incomplete and the species described so far are based on granule characters only. The granules are white.

1 *Indiella mansoni* Brumpt 1906
Indiella reynieri Brumpt 1906
3 *Indiella brumpti* Piraja da Silva 1919

D Genus *Ctenospora*

1 *Ctenospora libertonmenii* Chalmers and Archibald 1916
Ctenospora semoni Chalmers and Archibald 191
3 *Ctenospora clapieri* Montpellier Catanei and Clapier 1927

F Genus *Cephalosporium*

1 *Cephalosporium recifei* Leao and Lobo 1934
Cephalosporium sp Carrion 1940
3 *Cephalosporium granulomatis* Weidman and Kligman 194

Note Several attempts have been made to modify the systematics of the genera *Madurella* and *Indiella* The work of Ciferri and Redaelli (1941) and of de Mello (1947) should particularly be referred t

These diverse fungi have one feature in common namely the formation of characteristic granules in the parasitized tissues These are of definite form size and of variable colour The *Nocardia* species produce granules of the same microscopic structure as those of *Actinomyces israeli* in the classical actinomycosis and conform to the description already given These granules are white yellowish pink red or black The granules produced by fungi other than *Nocardia* are usually larger and are composed in the centre of a mass of segmented and branched hyphae which develop chlamydospores Chlamydospores are often found at the periphery of the granules Between the hyphae which make up the granule is pigmented amorphous matter which imparts the characteristic colour to the granule The shape of the granule may be oval round or vermiculate Colour of the granule cannot be used to classify the mycetomas However as a broad generalization white and yellow granules are produced by *Nocardia* or *Indiella* species or by *Allescheria boydi* while black granules are produced by *Madurella* and red ones most frequently arise from *Nocardia pelletieri*

Symptomatology

Most cases of maduromycosis are localized in the foot more rarely localizations are found in the hand leg forearm and even in the shoulder Typical Madura foot is a globose foot in which the normal plantar concavity has been replaced by a convex surface Three features characterize the lesions tumefaction fistulization and granules The first appearance is usually very slow and consists of a little papule or nodule which develops softens at the base and at length opens to the exterior The sinuses may be single at first but they usually continue to multiply and the discharge is oily and contains the characteristic granules The disease which in consequence of traumatic injection is at first confined to the subcutaneous tissue penetrates into all the tissues of the foot which it transforms into a mass of sclerotic tissue traversed by sinuses and sometimes cavities in which large masses of granules are to be found Several

years (10 to 15) are usually required for the full development of the characteristic Madura foot. The diseased foot may enlarge to a considerable volume so as to be scarcely recognizable; with, however, little sign of pain, the patient walks on a globose mass which serves as a support. His general condition remains satisfactory until such time as a secondary infection provides a complication.

Histopathology

Brumpt (1906) and Montpellier and Catanei (1931) give masterly descriptions of Madura foot. According to the last authors, the centre of the primary nodule is occupied by a granule of the parasite which is thus surrounded by a nest of leucocytes the component of which, all polymorphonuclear neutrophils, some intact, others pyknotic, are disseminated in a thin fibrous stroma. This leucocytic centre is in contact with a second zone rich in fibroblastic cells and neocapillaries of an inflammatory type, the openings of which are nearly filled with the tumefied epithelium. The inner region of this zone abounds in polynuclear cells. Large round or oval elements are also present measuring almost 40 µ with rather precise contours. Their nuclei have the structural characteristics of epithelioid cells. Often thrown back and depressed at the periphery, they are frequently single. However, bi- and trinucleate elements may be seen. The acidophilic protoplasm appears to be irregularly spongy; it contains up to ten polynuclear elements in various stages of lysis. The practically constant occurrence of these macrophages, sometimes seen at the periphery of the central leucocytic magma, imparts a distinctive appearance to sections, especially at low and medium magnifications. The fibroblasts increase in number in proportion to their distance from the centre; the tissue of the stroma, at first finely protoplasmic, becomes more dense with a fibrillar collagen; the polynuclear elements give way to mononuclears, especially of a plasmocytic type which are very abundant at the periphery. Disseminated eosinophils as well as histiocytes are rarely encountered. Pigmented cells, of which the pigment gives a ferric reaction, swarm in the second zone, apparently matching the fragility of the capillaries. The presence of giant cells, so constant a feature of other mycoses, has not been observed in this mycetomic tumour.

However, Brumpt and most other authorities consider the presence of giant cells to be a constant feature.

Treatment

If the condition is due to a *Nocardia*, treatment may commence with penicillin or sulphamides or a combination thereof. These medicaments are ineffective in the case of mycetomas caused by ascomycetes or *Fungi Imperfecti*, where an amputation sufficiently extensive to ensure the complete eradication of diseased tissue is necessary. Relapses are not infrequent.

Prognosis

This is always bad if not *good* ... at least so far as the diseased organ is concerned. Indeed so far as present knowledge goes amputation is almost always necessary.

Differential Diagnosis

Diagnosis of maduromycosis is so obvious that confusion with other diseases is likely only in the early stages. Nevertheless, syphilis and tuberculosis may present the same clinical picture though no other disease yields the triad of tumefaction, fistulisation and granules. Other mycoses (*blastomycosis, coccidioidomycosis*), *elephantiasis* ... *mossy foot* and *stat ... mycosis lymphatica* may also at first recall the picture of maduromycosis.

Mycological Diagnosis

This consists simply of finding and culturing the granules and is important from the therapeutic as well as the theoretical point of view. The grains are found by the naked eye or by means of a lens, then examined fresh or in potash. Very hard granules are softened in warm potash or boiling Eau de J... l. Before inoculation they are rinsed in sterile water.

Experimental Inoculation

The clinical picture of maduromycosis has never been reproduced from cultural isolates.

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CHAPTER XIII

White Piedra

THE WHITE PIEDRAS, sometimes called trichosporia or *piedra nostra*, are diseases characterized by rather soft whitish or brownish nodules which develop upon the hairs of the moustache or beard, more rarely upon the hair of the head or superfluous hair. The disease is cosmopolitan.

The irregular nodosities raise the cuticle of the hair and produce upon its surface a mosaic of vaguely quadrangular elements from to 4 μ in diameter.

The fungus which causes white piedra is *Trichosporon beigeli* (Rabenhorst) Vuillemin 190_, for which there are several synonyms:

Pleurococcus beigeli Rabenhorst 1865
Sclerotium beigelianum Hallier 18_8
Zoogloea beigeli Eberth 1867
Hyalococcus beigeli Schröter 18_6
Chlamydatomus beigeli Trevisan 1889
Trichosporum ovoides Behrend 1890
Trichosporum giganteum Behrend 1890
Trichosporum ovale Unna 189_
Trichosporon cerebriforme (Kambayashi) Ota 1928
Trichosporon granulosum (Kambayashi) Ota 192_
Trichosporon humahuaquensis Mazza and Nino 193_
Piedraia columbiana Dodge 193_
Trichosporon minor Iwasa 1940

Cream coloured colonies of *Trichosporon beigeli* grow easily upon Sabouraud's medium and have a membraneous and folded appearance. Microscopical examination shows numerous filaments bearing arthrospores in which they resemble *Geotrichum* colonies, and also appressoria which are not found in *Geotrichum* colonies.

Nodules of white piedra may be distinguished by their colour from those of black piedra, by their consistency being softer, and by the absence of ascospores in the knotted regions of the mycelium.

The best treatment would appear to be to shave off the moustache or beard, or if this drastic procedure is inconvenient, to apply sublimate (1 000) lotions twice daily.

Although white piedra has been known much longer than black piedra, from which they have been clearly distinguished only since 1911, the impression is that the former are much less well known than the latter and that there is need for clarification of the synonyms of the various species hitherto described. The rarity of the disease and its lack

of importance in human pathology tend to obscure studies of a primarily theoretical nature upon the causative agent

Redaelli and Ciferri (1941) have studied various fresh strains of *Trichosporon* and regard this genus as having affinities with the asporogenous yeasts taking its place with the sub family *Trichosporonoideae* (Nannf ld) Ciferri and Redaelli 1935 Diddens and Lodder (1942) regard the *Trichosporons* as anascosporous yeast like fungi which with the *Candida* and *Brettanomyces* species comprise the sub family Mycotoruloideae characterized by the formation of a pseudomycelium The sub family Torulopsidoideae in which no pseudomycelium is formed constitutes with the Mycotoruloideae the family Torulopsidaceae Langeron (1st edition of the *Précis de Mycologie* p 544) criticizes these authors for having taken as their type *T cutaneum* which is a common saprophyte and not a pathogenic *Trichosporon*

Redaelli and Ciferri (loc cit) give a list of nine pathogenic species of *Trichosporon* for whose pathogenicity we have little respect as follows—

1 *Trichosporon ovoides* (Mont and Vianna) Cif and Red
Trichosporon beigeli (Rabenhorst) Vuillemin
3 *Trichosporon Lucchetii* Red and Cif
4 *Trichosporon cutaneum* (de Beurmann and Gougerot) Ota
= *Hemispora coremiiformis* Moore
= *Trichosporon rugosum*
Trichosporon giganteum Behrend
6 *Trichosporon proteolyticum* Negroni and De Villa Lastra
7 *Trichosporon Balzeri* Ota
8 *Trichosporon granulosum* Ota
9 *Trichosporon ... ffred* Cif Cros and Brun

Langeron s words (1st Ed of the *Precis* p 546) provide an apposite conclusion Finally the white piedras are produced by a group of arthrosporic fungi equipped with complicated appressoria comprising species very close to one another and perhaps identical differing particularly in their geographical distribution Perhaps there is only one *Trichosporon* for white piedra ?

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CHAPTER XIV

Black Piedra

THIS INFECTION, characterized by hard black nodules along the length of the hair, is somewhat common in South America and has been recorded from Java and Cochin China. The fungus which causes it is *Piedraia hortai*.

The nodules may or may not be visible to the naked eye, but when the hair is combed they produce a gritty sensation. Several species of fungi have been held responsible for the infection but it seems likely that it is due to a single species, namely *Piedraia hortai* (Brumpt) Fonseca and Leão 1928. If infected hairs are examined in potash the nodules are seen to be below the cuticle and formed from thick mycelial filaments with brownish or blackish walls reduced to arthrospores. Among these filaments are found fusiform ascospores with a filament terminating each pole. The structure of the mycelial filaments complies with that which Arnaud named as co-stroma. The asci are apparently formed from one cell of the ascostroma which becomes ovoid or pyriform. The mechanism of liberation of the ascospores from the ascus is not yet known precisely but it is preceded by a gelatinization of the cell surrounding the ascus.

Inoculation of Sabouraud's agar with isolated ascospores or with nodules produces a black acuminate folded glabrous colony composed of thick mycelial filaments with short cells and many chlamydospores among which asci and ascospores may sometimes be seen.

The following are synonyms of *Piedraia hortai*:

Trichosporum hortai Brumpt 1913

Trichosporum paraguayae Delamare and Gatti 1928

Piedraia sarmentoi Pereira 1930

Piedra [illegible] Brumpt and Langeron 1934

Piedraia venezuelensis Dodge 1935

Piedra [illegible] Boedijn and Verbunt 1938

Diagnostic differentiation from trichomycosis or trichosporosis is easy. Treatment consists of rubbing twice daily with 1 : 2000 sublimate, or the hair may be shaved off.

Basing his work on Arnaud's thesis (1918), Langeron attempted to show (1929) that *Piedraia* is an Ascomycete genus belonging to the [illegible] *Pyrenomycetes*, order Microthyriales, and near to the family Microthyriaceae. The Asterinaceae as described by Arnaud form a group of parasites adapted to superficial parasitism. They require a very humid

climate for their de elopment and are only found in regions with high rainfall of a metre or more per year Langeron who with Brumpt described *Piedraia sarmentoi* (1934) as having 4 spored asci and squat ascospores finally believed (see 1st edition of *Précis d Mycologie* p 547) that this was borderline case of *P hortai* very closely related to this species and differing only in the form f the piedraic nodules the number f ascospores per ascus and the length of the pola filaments

The fundamental work on black piedra is that of Parreiras Horta (1911) which Brumpt cknowledged by deleting *Trichosporum hortai* (1913) which ultimately became *Piedraia hortai* (O da Fonseca and A E de Leao 1928)

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CHAPTER XIV

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Piedraia surinamensis De Lee 1935
Piedraia javanica Boedijn and Verbunt 1938

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The fundamental work on black piedra is that of Parreira Horta (1911) which Brumpt acknowledged by deleting *Trichosporum hortai* (1913) which ultimately became *Piedraia hortai* (O. da Fonseca and A. E. de Leão 1928).

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CHAPTER XX

Pityriasis Versicolor

PITYRIASIS VERSICOLOR is a cutaneous infection characterized by irregular scaly spots, fawn to brownish in colour and spreading over the trunk. On examining the scales a large variety of mycelial elements mixed with *rounded forms are found; the elements have been named M. furfur* (Robin) Baillon 1889 and are believed to be the cause of the infection.

Pityriasis versicolor has a number of synonyms: tinea versicolor, achromia parasitica of Jeanselme, pityriasis versicolor tropica, tinea flava, tinea nigra, body pot, etc. The disease has a world wide distribution and exhibits a preference for young adults but also attacks the very young and the very old. In temperate climates it is usually confined to the trunk and facial lesions are exceptional. In tropical climates facial localization is very common (Vanbreuseghem 1950). The infection may also attack the limbs, the neck and the scalp.

The spots of pityriasis versicolor are of varied and variable colour, sometimes darker, sometimes lighter than the surrounding skin; it is likely that the latter condition is due to protection of the skin from the sun by the scales. The outline of the spots is irregular, large or small and sometimes minute. The scales are fine and scurfy. On examination in chloral lactophenol, which is preferable to caustic potash as a clearing agent, rounded elements are seen of diameter 1 to 4 μ, after budding, arranged in clusters and mixed with mycelial fragments 3 to 4 μ wide and 1 to 40 μ long, sometimes branched. If the scales are stained before examination and not mounted in chloral lactophenol the mycelium is seen to be a much branched system which is considerably broken up into fragments upon the addition of chloral lactophenol or caustic potash.

Histological sections show that the filaments and spores are lying in the superficial epidermal cells and that here and there they penetrate slightly into the dermis.

The causal agent of pityriasis versicolor has been named *M. furfur* (Robin) Baillon 1889. In the literature the following synonyms are still found, e.g. *Microsporon furfur* Robin 1853, *Malassezia furfur* (...) Castellani 1908, *Malassezia tropica* Castellani 1909. But the name only covers a morphological entity, the picture presented by the scales is always the same whether in a tropical or a European case (cf. Le [illegible] one). It does not represent a biological entity, because it is not possible to culture the agent of pityriasis versicolor; when culture becomes possible several species may well be found, and as in the case of microsporum

hair the complex clusters of spores and filaments ma represent several botanically different species A number of ttempt to culture *Mala se ia f rfur* have failed However some workers namely Lanj (19?) and Moore (1941) claim to h e lt ined cultures and the la t named wa ab e to inoculate an animal Vanbreu eghem (19?0) and Lejeune (19 1) ha e



Fig 48

P yria s ve olo Small patches scat red on th ba k of a Negro

made repeated attempts on a larg sc le Vanbreus hem tried unsu cessfully with the following media S bouraud medium plain agar Loewenstein medium blood agar Loeffler medium Sabouraud medium with the addition of a fine layer f butter and direct inoculation of hairs n *vitro* Lejeune has had no gre ter success he repeated Moore ttempts and also tried the following media Moore medium plu penicillin Buller medium arious media in an atmosphere of 10 per cent or 20 per cent CO media enriched with urea and others with vitamin B respectively

On ccount of the failures t is impossible t speculat on the systematic position of the usal agent of pityriasis versi olor Micro scopical examination gives little indication of it position s th mycelium

a true one or a pseudo mycelium? What is the relationship between the mycelium and spore clusters? Different views rest on hypotheses rather than fact.

Vanbreuseghem (1950) turned his attention to the arrangement of the spores *en grappes*. With few exceptions the spores remain in aggregates and this undoubtedly indicates a particular form of growth which ensures that they adhere closely (myxospores) and probably indicates that they are in a common envelope or cell. Lejeune believes that this is not so in all cases because the elements of pityriasis versicolor develop between the cells and do not penetrate.

Diagnosis of pityriasis versicolor is easy by examining the scalp or the patient under a Wood light when certain elements not visible with ordinary light become apparent. Other diseases with which it might be confused are vitiligo, erythrasma, syphilis, Gibert's pityriasis rosea and seborrhoeic dermatitis.

Treatment consists in the application of ... 1 per cent alcoholic iodine, 1 per cent salicylated alcohol or Whitfield's ointment applied after a hot bath. Recurrence of the disease is frequent, no doubt because the apparent cure is rapid and a few small spots are often left.

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CHAPTER XXI

Rhinosporidiosis

RHINOSPORIDIOSIS is a disease characterized by polypous masses formed on the mucous membranes more rarely on the skin and it is probably a mycosis The causal agent has never been obtained in culture but has been named *Rhinosporidium seeberi* (Wernicke) Seeber 1912 According to de Mello (1949) the number of published cases in human beings totals 442 distributed throughout the world as follows Africa 1 N America 16 S America 34 Asia 377 (of which 103 are from Ceylon and 233 from India) Europe (Italy) Philippines 1 Of the cases from Asia (which constitute 85 3 per cent of the total) 52 7 per cent were diagnosed in India and 4 4 per cent in Ceylon According to de Mello the number of cases in animals is 70 of which 3 are from S Africa 11 from S America and 55 from India Thus rhinosporidiosis is primarily an Asiatic disease Conant *et al* (1947) reported the occurrence of rhinosporidiosis in Scotland and England but the case reported by Ashworth to which they no doubt referred was of an Indian student at Edinburgh

The disease affects young adult males In India it is especially noticeable among those employed in lifting sand and gravel from river beds It is possible that rhinosporidiosis is an infection of fish which will accidentally attack man and domestic animals In an infected frog (*Hyla rubra*) Carini (1940) described *Dermosporidium hylarum* a parasite resembling *Rhinosporidium seeberi*

The parasite described by Seeber in 1900 has the following synonyms—

Coccidioides sp Wernicke 1900	*Rhinosporidium kinealyi* Allen and Dave 1930
Coccidium seeberi Wernicke 1900	Dave 1930
Rhinosporidium kinealyi Minchin and Fantham 190	*Rhinosporidium ...* Aben Athar 1944
Rhinosporidium equi Zschokke 1913	and probably *Dermosporidium hylarum* Carini 1940

It must be realized that the singularity of the causal agent of rhinosporidiosis based as it is solely on morphological consideration is not as conclusive as it would be if the parasite could be cultured The phenomenon of convergence which is so common in parasitic fungi precludes the conclusive demarcation of a species on unique morphological features alone Proof that this is so is given by the fumagoid forms which appear in the tissues after parasitization by several species of *Phialophora* responsible for chromoblastomycosis and also by the better known

example of the dermatophytes which have a great number of species but apparently only one morphological parasite with little variation

All attempts to culture *R. seeberi* and to inoculate man or animal have failed

It has been stated that rhinosporidiosis is characterized by polypous masses these may be sessile or pedunculate and in 50 per cent of the cases are developed on the nasal mucosa The conjunctiva of the eye is also frequently infected Polyps have also been recorded on the pharynx larynx urethra vagina sometimes on the skin and in one case in the brain

The polyps are red crumbling masses which bleed easily On their surface white marks indicating the presence of the parasite can be recognized

In its youngest stage the parasite is a round corpuscle greater in size than an erythrocyte (7 to 8 μ diam.) and [illegible] a nucleus and lipoid reserve. *It has a thin chitinous cell wall. This wall thickens and* becomes double owing to the formation of a cellulose membrane and the cell attains a diameter of 50 to 60 μ when the nucleus divides. The nuclear division is repeated without cleavage of the cytoplasm [illegible] such cleavage only takes place when the corpuscle has attained a diameter of 1 0 μ and contains about [illegible]000 nuclei The parasite continues to [illegible] until it has attained a diameter of 300 to 350 μ then its contents [illegible] through a pore in the original cell membrane The spores are discharged by the sporangium [illegible] into the surrounding tissues or the natural cavities such as the nasal cavity or the conjunctival cavity where they [illegible] those of neighbouring sporangia But it is preferable to carry out diagnosis by the microscopic examination of fragments of polyps [illegible] under a cover slip

The polyps are produced as a reaction of the conjunctiva [illegible] the sporangia [illegible] infiltration of lymphocytes and plasmocytes [illegible] more rarely involve polynuclears Around the membrane of discharged sporangia granulomas may be developed with giant cells

Treatment of rhinosporidiosis consists of surgical removal [illegible] followed by electrocoagulation Various medicaments with [illegible] of trivalent antimony have been applied without success [illegible] antimony compound (neostibosan) has proved useful [illegible] Rhinosporidiosis in domestic animals produces similar symptoms to those found in man The disease is known to attack horses mules and [illegible]

The systematic position of *Rhinosporidium* [illegible] Ashworth (1923) stated the organism to have affinities with [illegible] Ainsworth (1949) places the parasite among Phycomycetes

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CHAPTER XVII

Sporotrichosis

Definition

Sporotrichosis is a benign but chronic mycosis attacking the skin and sub cutaneous tissues and forming ulcers which extend along the lymphatic ducts. The infection is caused by traumatic injection of *Sporotrichum schenckii*.

Historical

This may be divided into three very unequal periods during which the principles were discovered leading to our knowledge of this infection. Chronologically these periods are—

1. The American period
2. The French period
3. The South African period

The first was a period of discovery, the second was of a descriptive nature and laid the foundation of our present knowledge, and the third was one of confirmation and integration of concepts and of the posing of new problems.

1. *American Period.* In 1898 in the United States Schenck described the first case of sporotrichosis; two years later Hektoen and Perkins discovered another case and gave the name *Sporothrix schenckii* to the pathogen previously isolated by Schenck.

French Period. This period commenced in 1903 with De Beurmann and Ramond's discovery of a case of sporotrichosis. M. Beurmann and Ramond named the causal agent *Sporotrichum beurmanni* in 1903 and considered that it differed from the American sporotrichosis which De Beurmann and Gougerot in 1906 had named *Sporotrichum schenckii* (Hektoen and Perkins 1900).

The initial stimulus to the study of sporotrichosis in France and elsewhere was given by the work of De Beurmann and Gougerot and especially by their publication of a very important monograph entitled *Les Sporotrichoses* (1912). This noteworthy work emphasized on the one hand the diversity of the fungi responsible for sporotrichosis and on the other the serious nature of certain forms of this mycosis. The ideas put forward were taken up again much later by Gougerot (1930) and, as we think

resulted in misunderstanding of the nature of sporotrichosis in Europe and especially in France where it is a relatively frequent and serious disease and the nature of the same infection in other countries notably North America It is probable that at the time when De Beurmann and Gougerot wrote a large number of unsuspected cases of sporotrichosis dealt with by mistake for other diseases had imparted a very grave clinical impression However this does not cover the whole question We believe at the time of writing that it is wrong to postulate the existence of one sporotrichosis specific to Europe and another confined to America

3 *South Africa Period* This commenced in 1927 with the work of Pijper and Pullinger who studied an outbreak of sporotrichosis among South African native miners The period really began however in 1947 with the publication of a symposium entitled *Sporotrichosis Infection in Mines of the Witwatersrand* which reported observations made on 3 000 cases of sporotrichosis diagnosed in both natives and Europeans in less than two years It did not contribute anything fundamentally new but it confirmed and extended what was already known and suggested that the infection is caused by a fungus that normally lives saprophytically on vegetable matter It also raised interesting problems such as for example the parasitic cycle within the host tissues

It must be realized that this conception of the history of sporotrichosis in three periods is purely arbitrary

Importance and Geographical Distribution

Sporotrichosis is a relatively rare though cosmopolitan disease This is found to be especially true when it takes the form of an epidemic The adult male is apparently most susceptible no race is immune but contraction of the disease depends on individual resistance Men of certain occupations are more likely to be infected than others Small epidemics have been noted amongst florists The example already mentioned in South Africa shows us a vast epidemic that broke out among miners black and white alike In France many cases were recorded during the early years according to De Beurmann and Gougerot seven years after the first observation of De Beurmann and Ramond more than 200 cases had been discovered In actual fact according to our information the disease is rather rare and we have reason to believe that it is because the infection is not well known that recorded cases are few

Etiology

The etiology of no mycosis is better known than that of sporotrichosis *Sporotrichum schenckii* lives saprophytically on various plant materials living or dead If a man or an animal receives a slight wound the organism enters through the skin

The first important step of this demonstration was made by the discovery of Gougerot (communicated by De Beurmann and Gougerot in 1908) He

discovered in the French Alps strain of *Sporotrichum* on the bark of a beech tree the leaves of a horsetail and dry grains of oat These strains were *indistinguishable* from those of *S beurmanni* their pathogenic power at first poor in the rat subsequently increases Cougerot gave a diagram (p 1 4 *Le Sporotrichoses*) of a *Sporotrichum* growing on an oat gram which was as perfectly developed in all microscopic characters as a culture produced in the laboratory As a result several small epidemics were produced by handling plant and Foerster (19?6) was able in 1? cases to infect Barberry by way of it spines Benham and Kesten (193?) after having isolated non pathogenic *Sporotrichum* from different flowers tried to infect carnation buds with *Sporotrichum schenckii* The conclusion that may be drawn from this experiment is doubtful because even if the authors were able to re isolate *Sporotrichum schenckii* from the decaying carnation bud as a result of the previous infection it does not necessarily follow that the pathogenicity of this fungus had been demonstrated for carnation for as Skinner Emmons and Tsuchiya (1948) have pointed out it is generally accepted that *Sporotrichum schenckii* is able to develop on dead or decaying vegetable matter

According to the South African workers (cf Symposium) sporotrichosis always followed a slight skin wound However of 8? cases recorded at Venterpost and at Consolidated Main Reef (411 and ?64 cases respectively) only 1 per cent and 40 per cent respectively of the workers recall having been wounded Nevertheless the workers most frequently attacked are those who are exposed to slight injuries during their work Furthermore in experiment carried out on volunteers it has been *demonstrated that Sporotrichum schenckii is capable of infecting the* skin other than through an abrasion or where it has been irritated by hot dressings or severe rubbing even though the skin may not actually have been broken In the mine it is on the sound untreated wood used for props that *S schenckii* develops In practice this is the only important source of infection *S schenckii* has only once been isolated from the air and *never from the ground or from water The South African authors have* also demonstrated that flies (*Musca domestica*) become infected after contact with patient bearing sporotrichosis lesions They have shown that *S schenckii* can be isolated from the feet and from the faeces of these flies Also the fungus is able to live for several days within the body of the fly but it is generally accepted that in practice flies do not play an important part in transmission *of sporotrichosis*

Pathogenic Agent

The causal agent of sporotrichosis is *Sporotrichum schenckii* (Hektoen and Perkins 1900) De Beurmann and Gougerot 1908 In 1903 Matruchot and Ramond reported the existence of a new species isolated from the first European case by *De Beurmann and Ramond and named Sporotrichum beurmanni* The distinction into two species is based on the fact that the colonies developed by the parasite isolated by Schenck were white

while those isolated from the French case were black Davis however (1913 1917) showed that littl value could be attributed to a difference of pigmentation or to a difference in capacity to ferment sugars Most authors agree that there is but one causal agent of sporotrichosis *S schenck i* and this agent exhibit certain variations in pigmentation and fermentat e action There is a considerable number of synonyms

Sporothrix schenckii Hetkoen and Perkins 1900
Sporotrich m beurmanni Matruch t and Ramond 1905
Sporotrichum asteroides Splendore 1909
Sporotrich m jeanselmei Brumpt and Langeron 1910
Sporotrich m carougeaui Langeron 1913
Sporotrichum councilmanni Wolbach Sisson and Meier 1917
Sporotrichum lipsiense Benedek 1920
Sporotrich m epigaeum (Brunaud) Aschieri 1929
Rhinocladium schenckii Brumpt 1930

The Nature of the Parasite in Pus and Tissues

According t classical opinion research on the parasit in the pus or tissues of man remain for the most part non xistent But en if such research is often f little value and does not constitute a sure diagnostic method it is incorrect t say a some workers do that it is impossible t detect the parasite in the pus by direct examination (Gougerot 1936) De Beurmann and Gougerot were the first t describe the tissue form of the fungus (1906) and Gougerot reconsidered the question in 1909 These tissue forms are described as boat or cigar shaped The organisms are elongated bodies with rounded end about to 3 μ wide and 3 to 5 μ long in which the protoplasm i concentrated t the tw extremities These bodies occur only rarely in men but are encountered abundantly in the pus of inoculated animals (rat) They are intracellular in the leucocytes or giant cell thus causing them to become ery ti htly packed

A rarer form of *S schenckii* both in man and animals is an asteroid form first described in 1908 by Splendore who discovered it in an infected woman in Brazil It w this particular form which Splendore belie ed to be a new species and which he named *S asteroides* Tálice (193) reported the same steroid form in two infected people in Uruguay Two more cases w re disco ered in North America by Moore and Ackerman (1946) and Pinkus and Grekin (1950) Asteroid forms hav been seen by De Beurmann and Gougerot Greco Harter and Gruyer (1900) in a guinea pig Talice described the asteroid forms as follows Extracellular bodies surrounded by pyocytes irregularly rounded rather small the greatest diameter not xceeding 10 μ Its structure is characteristic in the centre is a round corpuscle (spore) μ in diameter the contents staining a diffuse blue iolet colour with haematoxylin and ha ing distinct double wall which takes up a deeper violet coloration The surface is co ered with radially arranged protuberances of ery variable length (between 2 to 3

and 7 to 8 μ) The c projections spread in all directions They seem to have the central body at varying levels and it is the e structures which give the spore it a teroid or sweet chestnut like appearance These bodie tak up eo in v ry strongly thus indicating their acidophilic nature Langeron (Talice 193) re arded the c form a imple granules

Splendore has shown by cultural method that these a teroid form are capable of reproducing the fungu in its more u ual form and that th y constitute a stage in the parasitic state of *Sporotrichum*

Until just recently asteroid forms were considered t be rare How r the observation of the South African workers ju tify a recon ideration of this view They found a teroid forms in no less than 1 of the ca e on which they were working and starting with South Afr an or North American strains reproduced th m in animal Their conception of the parasitic cycle of S ech ncki i as follows—

Stage 1—Repre ented by the boat like f rm or cigar bodie which resemble spores produced in culture by S *ncke clu* Both spores and ci ar bodies react identically to Gram s tain staining only slightly

Stage —Certain boat like form are tran formed into cryptococcu element with a spherical form

Stage 3—Repre ented by an increa in ize of th cryptococci t twice their original dimension

Stage 4—Th periphery of the bodie becomes covered with an eosinophilic coating

Stage 5—*Il pre ented by the ast roid bodies with a central m —the* cryptococcoid body—surround d by delicate rad ting eosinophilic projections which are ea ily destroyed during manipulation

Asteroid bodies appear t ward the ixth we k aft r the init l natural or experimental inoculation at this st ge the r bod an l cryptococci are rare or lacking

It is difficult to draw satisfactory conclu ion Are the ob rvati of the South African work rs due to biologi al p culiariti in the which they have studied? Or have their ob rvations been more critical becau e they have taken into account the extreme frailty f the m m upon which they worked? W cannot say for certain Suffice it t that their description of the a teroid b dies corre ponds v ry closely with that given by Talice and the b unt

N mycelial element are found in pu r in ti ue Fra ment f mycel m injected into ti ue experimentally rap dly di ppear n l only the spore appear to d lop int boat form

Macroscopic Nature of Cultures

On Sabouraud glucose a ar at room t mp rature (C) t mi f S *schenck* appe r on the third or fifth day aft ne ul ti n w th p Their app arance is ab olut ly diff rent from that f m ol 1 t fr m other pathogenic fun i l cause th colonies n n t know They ppear

as small smooth white round plate lry or moist and somewhat re embling yeast colonies In certain strains the whit pigment tion persi t indefinit l but often after a f w day it becomes brown h or black It will be realized that it wa on the ba is f thi lifference i pigmentation that *S schenck* nd *S be rma* ni were separated A they grow older the colonie become more m ist and the surface l comes corrugat l and often covered with wick lik protrusions The colonie are of an el tic consist ncy

Davis bout 1913 w able to prod ce the boat shaped bodies which characterize the ti sue form f *S schenck* *i tro* either by culturing it anaerobically or by including a piece of fresh sterile imal tissue and using blood or serum the medium More recently Campbell (194) obt ined the Yeast like ph se i the boat shaped phase by culturing *S schenck* at 37 C under anaerobic conditions on Francis med um (blood ag enri hed by gluco and cystine) On this med um colonies appear after 36 t 48 hours like small yellowish bacterial growths consi ting of elongated igar lik bodies which reproduce by budding from one of their xtrem ties These bodie show a Gram po iti reaction This form last for long tim f the ulture on Franci med um is kept at 37 C If the cigar like bodies are kept t C on Sabouraud s medium they reproduce the mycelial form The ch nge from the mycelial t the yeast like phase from cultures maintained for some time in the laboratory requires several transfers

S schenck will f rment gl co g l ctose laevulose and maltose but not dextrin mannitol or d lcitol Its action on the f llowing substances is variable ccharose lactose in lin starch and glycerine (Marroquin 1947)

Macroscopic Nature of Cultures

It is not propo ed t ref r again t the yeast lik phase de cribed bov The mycelial ph i made up of mycelial filament spores and rarely hlamydospores The hyphae ha a diameter of something under μ they are hyaline multicellular and branched The spores are borne on branch filaments upon the surface f the medium either terminally or around the articulations of the hyphae They are borne singly on sterig mata l t 2 μ in length and bout 0 5 μ in width but at the xtremities of the hypha the e spores are aggregated t form an oval mass about 1 μ in diameter The spores may attain a length of 3 to μ and a width of to 3 μ they may be brownish but are never black Once detached from their parent mycelium they reproduce by budding It is actually extremely difficult t make out the relationship of the spores with the parent mycelium when examining part of a culture teased out on slide The best preparations are obtained in practice by culturing the fungus directly on the slide or more simply De Beurmann and Gougerot long ago realized by dropping a coverslip on the surface of the colony The co er slip is raised at a con enient opportunity and the material adhering to it is fi ed and stained

It is important to remember the impo ibility of diagno i in the va t majority of cases where there is not access to histological method there is a tendency to reject a diagnosi of mycosi though the histopath lo i al picture is not conclusive in that the pathogen has not actually been seen *in the ti sues The simpl st method of diagnosis and which gives the best* and most con tant result is that of culturing the fungu

Treatment

Sporotrichosis has a unique position amongst therapeutics it re en iti *to one medicament only namely pota ium iodid* Antibiotics such a streptomycin and penicillin have been applied without success

Cou erot prescribed _ g *for the first day 4 g for the third and fourth* days then 5 or 6 g per day as the dose to be taken daily before meals

Conant *et al* gave 10 drops of a saturated solution of pota ium iodide three times a day and increased each do e by 5 drops three times a day until it had reached 30 or 40 drops three times a day The drops are administ red before meals and diluted with milk or water *Intravenous* injection of 1 g p d of sodium iodide may be applied in place of potassium iodide ingestion

The South African authors who have treated a great number f cas in their country adopt the followin method for the first two d s at the hospital the patient receive _ g (30 grains) of pot ss ium iodide three time a day in a soupspoonful of water (½ ounce) They consider that if the *symptoms of iodine poi oning are to appear they will do o durin this* time If the symptoms are slight the treatment is continued without int rruption If they are serious the treatment is stopped for 48 hours and then resumed The size of the dose is generally maintained at the initial lev l but may be raised until the daily dose totals 1 0 grains (0 g)

The iodide treatment should be continued for 4 to 6 week fter apparent recovery The treatment i s ry eff ctive

It is not advisable to inci e the lesion becau e this oft n l d to long term ulceration Spontaneou ulc rs can be treated with iodine In in In c rt in cases it i an advantag to use an auto or a stock accine n patient who are not sufficiently r sponsive to iodine

According to the South African work rs a on ltion f thyl hloride applied to the inocul tion hancre m y eff ct a cure econd ry nodul are not however aff cted by thi treatment

Prognosis

It c n be id of practic lly ev ry case th t prognosis is g l f spontaneou ure and naturally resi t nt individu l are kn The s ceral forms and certain f the mucous m mbrane lesion ha r fit l f rtunat ly thi u pt xceptional

Differential Diagnosis

The localized lymph ngitic f rm is diff ult t c nf se w th n ther H wev r th primary l sion mu t be di t ng ished from s ph b

tuberculous impetigo ecthyma and tularemia Of other mycoses chromoblastomycosis coccidioidomycosis North and South American blastomycoses and trichophytic granulomas may be confused with sporotrichosis

Mycological Diagnosis

Although theoretically there are three methods of mycological diagnosis namely examination of the pus culture and animal inoculation culture remains the most trustworthy and constant method

(a) Examination of Pus

Pus is obtained either from softened nodule or from the exudate of the primary lesion and is examined for the presence of boat shaped and asteroid forms In man the boat shaped forms had always been considered rare and the asteroid forms exceptional until the observations of the South African workers

The boat shaped and asteroid forms can be examined directly on slide under coverslip For the boat shaped forms Area Leao and Coto (1940) recommended staining by the May–Grunwald–Giemsa procedure Staining is carried out on smears of pus diluted in 10 to 1 volumes of sterile water the staining time should not exceed 30 min By this method the Brazilian workers have been able to recognize not only the boat shaped forms but also the budding forms

(b) Cultures

The cultures are grown on Sabouraud medium at temperature of —° C A few large drops of pus taken from an unopened nodule by a syringe are spread over the agar surface After 3 to 5 days the characteristic colonies appear Campbell (194) was able to produce the boat shaped forms on Francis medium at 37 C

To facilitate a rapid diagnosis Gougerot has devised a contrivance for running the pus on a dry glass tube This method consists in allowing a large drop of pus to run along the wall of the tube in the angle formed between the agar surface and the wall when inoculating the agar These parasites develop on the glass through which it is easy to see and examine them on the second or third day (Gougerot 1936) For this purpose the tubes are fixed with Plasticine on the stage of a microscope and examined under a powerful eyepiece and a low powered objective

The South African workers have found that most of the lesions give negative cultures after 400 grains (about 26 g) of potassium iodide have been taken

(c) Experimental Inoculation

The best experimental animal is the male white rat The pus or an emulsion of the culture is injected intraperitoneally There is rapid development (in week) of an orchitis and peritonitis characterized by

little white nodules spread throughout the mesentery and the peritoneum. Examination of the secretion reveals the presence of numerous boat-shaped Gram-positive intracellular bodies.

Resuming the experimental study of sporotrichosis in the mouse, Baker (194) showed that in this animal *S. schenckii* causes the development of a disease so chronic that it is usually fatal. In the tissues of the mouse are found vast numbers of boat-shaped bodies.

Serological Diagnosis and Allergic Reactions

1. *Widal and Abrami. Sero-diagnosis.* About 1908 Widal and Abrami applied an agglutination test to the diagnosis of sporotrichosis.

A spore suspension is prepared by removing fragments of a 4 to 1 weeks old culture. The fragments are ground up in a mortar, diluted with sterile water and the suspension is then filtered. The filtrate is examined on a slide to ensure that it is rich in spores but contains no mycelial filaments. *The suspension is agglutinated by serum from patient infected* with sporotrichosis for 15 to 60 minutes at dilutions ordinarily of the order of 1/100 to 1/400 but which may go as far as 1/800 and beyond. In fact the carrying out of this procedure is not so simple as may at first appear; it is difficult to obtain a *homogeneous spore suspension* and many cross reactions have been observed. This method is inferior to diagnosis by culture.

The same may be said of the *complement fixation reaction*.

3. The following reactions have also been studied and found to lack specificity: the *cutaneous reactions* (Bruno Bloch), the *subcutaneous reactions* (Pautrier and Lutembacher), the *intra-dermal reaction* (De Beurmann and Gougerot).

Spontaneous Sporotrichosis in Animals

Sporotrichosis has been recognized in a large number of animal species including the rat, dog, cat, rabbit, horse and mule. Lutz and Splendore (1907) were the first to describe spontaneous sporotrichosis in the rat. In *this animal the lesions are sub-cutaneous and articular*, the paws and tail being most often attacked and the infection here taking the form of tumefactions filled with cheese-like pus. Visceral and generalized lesions have also been recorded.

In all the animals affected the tissue form of *S. schenckii* is more frequently encountered and in much greater numbers than in man. It is believed that in the rat the disease is transmitted from one animal to another by biting, but this requires confirmation. It seems rather unlikely from what we know of the aetiology of sporotrichosis in human beings.

Treatment of animals, as of man, involves the *application of potassium iodide*. Carougeau has demonstrated the great value of this therapeutic method in horses and mules (1909).

Cases of transmission of sporotrichosis from animal to man have been recorded (Gougerot, 1909).

Prophylaxis

The course tak n by a sporotrichosis epidemic and the experience acquired by the South African authors on the subject have given valuable information on the essential facts

As already st ted sporotrichosis usually occurs a isolated cases or more rarely in the form of small epidemics amongst for example florists In this case fter diagnosis therapeutic treatment is begun No special precaution is taken to pre ent transmission t other individuals and as far as is known no case of contagious spread amongst human beings has been described

This is not the case when sporotrichosis attacks a large number of people and when ideal conditions for it spread are realized The various epidemics in the South African mines (Witw tersrand) are believed to be rare xamples but are so important that they merit special attention From the admirable series f b ervations and xperiments made by South African specialist it is known that spread of such an epidem depends on the following factors—

1 A patho nic agent Sporotrich m schencki
 A vegetable substrat m for the de lopment of th pathogenic ag t wood in the mines
3 A li ing organism recept to the parasite man
4 An abrasion or wound

Each of these factors is considered individually in relation to the hygienic preventiv ction th t may be taken a follows—

1 The Pathogen

Although a large number of other fungi ha e been isolated it is estab lished that all cases of sporotrichosis cited in the mines of Witwatersrand were caused by the one pathogen S schencki (based on an identification made by Emmons who alled the parasite S beurmanni) Of 2 000 samples from sporotrichosis ictims 1 400 yielded S sche cki in culture

2 Wood in the Mines

S schenck in the mines f the Witwatersrand li es saprophytically upon the wooden props It development on these props depend on various conditions—

( ) The wood must be of a certain type Different species of eucalyp tus an acacia widespread in South Africa (*Acacia moll ssima*) known as the wattle nd arious pines are suitable for the development of *S schenck* However the fungus will not grow on the Oregon Pine (*Pseudotsuga taxifolia*)

(*b*) The wood must not ha been treated by chemicals but may have been subjected t different stages f seasoning (g desiccation et) without affecting the multiplication of the fungus

(c) The wood must be healthy. The formation of mould on the wood reduces the development of *S. schenckii* considerably for reasons not yet understood. Among such antagonistic species are included *Fomes* sp., *Hydnum* sp., *Lentinus lepideus*, *Polyporus rugulosus*, *Poria* sp., *P. vaporaria* and *Stereum spadiceum*. Certain species such as *Coniophora cerebella* have no antagonistic action. The destruction of *S. schenckii* by these fungi takes several months but is usually almost complete after 4 months. It should be noted that if rotten wood is sterilized it may become reinfected by *S. schenckii* but the development of the pathogen under such conditions is poor.

S. schenckii grows most easily on white wood from the heart of the tree. Its penetration into the wood never exceeds 1 to mm but in transverse section the organism may be found at certain points up to 2 cm deep; thus though it has no great power of penetration it is able to gain ingress via any fissures which it may encounter.

The nature of the fun u varie according to the species of the t w l but the colour of the colonies is usually grey, ochre or blackish. On some species of wood the colonies are v cous on others th y re mble milk of lime being damp and growth. When the wood is desiccated the colonies have a sooty appearance. It is impossible to recognize with certainty colonies of *S. schenckii* by macroscopic observation alone. The South African authors have said that the spores of this fungus are triangular, the sides of the triangle varying in length from b μ t μ. By ob ecting scrapings from infected wood to microscopic examination it is easy to recognize the triangular spores which the South African authors have a diagnostic value. That the strain isolated from the props was in fact the pathogen was demonstrated by the inoculation of volunteers.

3 Man

The numerous cases of spontaneous sporotrichosis in native and European workers in the mines of the Witwatersrand and the inoculation of volunteers have provided ample evidence that the mines possess pathogenic strains of *S. schenckii* developed on the props. A few cases of natural immunity have been recorded by inoculation which were not followed by infection.

4 Wounding

Although no apparent wound was found in a limited number of cases, experiment has shown that an abrasion is necessary for the transmission of sporotrichosis in the presence of *S. schenckii* itself.

It is now established that all the factors are necessary. It is impossible to take an one of them and the fruit th t f pad m in practice two of the factors are not controllable: man and wounding. Of the other two factors *S. schenckii* the

wooden props—which would be the more profitable to tackle? The introduction of the fungus into the mines could not be checked becau e it is not known how it is introduced though it may possibly come from infected individuals It h s indeed been found possible to contaminate wood with human pus Once the wood is contaminated natural vectors ther than m n (g w t r insects) suffice to transmit the fungus from conta minated to new wood It seems cert in on the other hand that it was not the new wood wh ch introdu ed the fungus into the mine because wood has never been found to be cont minated before it enters the mine Inf st tion of the wood by the patho en can l controlled directly by spr ying cont minated wood with fungicide or indirectly by treating the wood with fungicides before it is introduced into the mines or after it has l n introduced but is st ll uncontaminat d Both method h s been succes fully employed

Impregnation of the wood is eff cted by spray ng with a m xture (Y rd Mixture) containing 3 per cent zinc lphat and 0 3 per cent Triolith (product composed f sodium fluoride dinitrophenol and potas ium dichromate)

Spraying with Dowicide (containin sodium pentachlorophenat) nd w th pentachlorophenol wa al eff ct

By deciding to use only previously treated wood the South Africans ha been able t control epid mics successfully and qu ckly

Taxonomy

In this ch pter the binomial *Sporotrich m sch nck* has been accepted t designat the pathogenic agent pecifi to sporotrichosis According to Vuillemin howe er the gen *Sporotrichum* adopted by Matruchot f r the pathogen discovered by D Beurmann and l amond (*S be rm*) loes not describe the p tho en of sporotrichosis which should be placed in the genus *Rh nocl d m* This view wa t ken by Brumpt In 19— Langeron wrot There are indeed two parallel series of sporotrich one of them is in the Mucedineae nd in part compri s the genus *Sporotrich m* Link 1909 w th diffuse mycelium no diff rentiated conidiophores the conidia bein borne directly on the mycelium or more rarely on small sterigm ta nd in part the genus *Rhinocl d um* Cord 1837 which diff rs from the forme by the possession of di tinct septat conidiophores at the end of which are projecting teeth bearing th conidia The othe series in the Dematieae compri es the two genera *Trichosporium* Fries 1849 and *Rh nocl d um* Sa cardo and Marchal 188 *Trichospori m* orrespond to *Sporotrich m* with diff se mycelium conidia usually sessile and borne irre ularly along the filament *Rhinocl d um* is homologous w th *Ph notrich m* differing in that t has no differentiated conidiophores nevertheless it ha the characteristic teeth and the dusky appearance

It would pp ar to be difficult t assign t the genus *Rh nocl d um* a parasit such s *S sch nck* which is not an authentic member of the

Dematieae and which also vary variable in spore colour and has a hyaline mycelium. On the other hand it must be admitted that the position of the spores is extremely variable in S. schenckii. However the name S. schenckii in addition to actual priority and to the fact that it is appropriate to the disease to which it gives rise has been adopted by so many authors that to avoid confusion it seems preferable to retain it.

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